PREPARATION FOR THE PROFESSION *

The Present and the Future

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THERE are periods in the history of every country when the form of medical education is appropriate to the pattern of medical practice, and when that pattern is itself suitable to the medicine of the day, so that all knowledge can be applied effectively and ethically. The standard of medicine is then as high as the degree of knowledge will allow, for medicine is in balance.

Such a period comes to an end when there is a major advance in medical knowledge. This advance passes very rapidly into practice and changes the pattern of it. The change of practice then alters medical education, and if all goes well balance is restored.

It is our particular good fortune to belong to medicine when it is again changing, or to be accurate has just changed. The increase of knowledge has enforced specialisation—which itself ensures that knowledge will continue to grow at speed. But, because in Britain no-one now lives far from a specialist, the general practitioner is prevented from doing much of the therapeutic job he was trained for. Instead, he is left with an overwhelming amount of other problems of diagnosis, treatment, and prevention of disease, for which he was not trained. He must transfer many patients to the care of another doctor, and he must be sure that he chooses the right specialty.

While this increase in knowledge has thus been altering the pattern of practice, a change in the quality of knowledge has altered the doctor's concept of disease. His attitude to diagnosis and treatment has become more scientific.

But it must be noted that the change is in attitude to disease and not in attitude to the patient. The problem of medical education is how to inculcate the scientific attitude while maintaining the highest standard of clinical skill and the most humanitarian concern for the patient as a person.

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It took us quite a long time to accept that with the coming of specialisation had come the end of general practice as we knew it, and also the end of the apprenticeship training which it had evolved for itself. During that time an inevitable disruption of medical education has been intensified, more in some schools than others, by our continuing to produce general practitioners of a kind no longer required, by a system of apprenticeship to specialists which could not be successful anyway.

However, that era of uncertainty as to the aims and objects of medical education is over. It ended, in fact, several years ago when the General Medical Council in its *Recommendations* of May, 1957, officially stated that the aim is no longer to produce, by the time of qualification, a finished doctor of any kind. In future medical education, for family doctors as well as for specialists, is to consist of two portions, undergraduate and postgraduate. The significance of this radical change has not yet been fully appreciated for several reasons. One is that a year of internship after qualification had become compulsory before 1957, and therefore the G.M.C.'s action appeared to some to be no more than giving official blessing to something which had already happened. A second is that, because medical education in this country is very rarely the primary concern of anyone, very many of those actively engaged in it have not yet read the G.M.C.'s recommendations. A third is that, in contrast to all its previous announcements, the G.M.C. did not specify in detail the nature of either a minimum undergraduate education or a minimum postgraduate training. It very wisely left the onus of creating a new pattern of undergraduate education to each individual university and medical school, stating that this pattern must provide a sound basis for further study, by ensuring that the student not only acquires knowledge and clinical skill but also scientific method; he is to be given an education as well as a training. This freedom is obviously essential if each of our 26 schools is to be able to develop new enterprise to the best of its capabilities; but initially of course it can act as a stimulus to progress only in those schools where the desire for progress exists.

Thus, though medical education in this country has passed out of the phase of catabolism into the phase of anabolism, the signs of this are not to be seen in every university. Some schools have set a new course for a new educational objective and are under way; some are drifting out of control; some are in the doldrums, and some are being blown far off course—even off their original course—by the contrary winds of contemporary medical practice. It is inevitable that some will have a greater proportion of teachers who are firmly attached to the old form of training; but it is equally inevitable that these teachers, by their resistance to change, will demolish the pattern they seek to preserve. It is natural that those schools which have been most successful in the application of one method should be the last to realise that it does not work any more. The man who has for years travelled to his destination in a Rolls-Royce does not think of getting rid of it—until he discovers that others are getting there more satisfactorily in an aeroplane—with Rolls-Royce engines, of course.

There is therefore cause for neither surprise nor lament in our present state of medical education, save in one respect. Speed of adaption is obviously important and it does appear that this could be unnecessarily slowed in London. About half of our medical students receive at least their clinical training in the 12 London medical schools. Inequitable as it may seem, a faculty which has 12 separate schools is unable to move 12 times as fast as other universities, and is more likely to resemble a convoy whose speed is always that of the slowest ship. It is always difficult for the commodore of a convoy to give the order "All ships to proceed at their best speed". It is true that in this case precisely that order has been given to the whole medical-education navy by the G.M.C.; but there is in this country a well-known precedent for turning a blind eye to the receipt of a naval signal.

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* Extracts from the Wood-Jones lecture delivered in the University of Manchester Medical School on Feb. 9, 1960. An abridged version of the lecture appears in the October issue of the *Manchester Medical Gazette*.

However, all schools have been charged with the duty of adapting their education to meet modern conditions and needs, and most have already begun to do this.

At first sight they appear to be up against an insuperable difficulty—that of deciding how much knowledge and how much training is to be in the undergraduate years, and how much in the postgraduate. These questions seem difficult to answer in view of the fact that the responsibility for the postgraduate years is shared by the university with many other organisations, including the Royal Colleges and the Ministry of Health, and no one of them has sole authority. Furthermore, nobody could at the moment be precise as to how much knowledge and how much technical skill is necessary for the minimum effective practice of any branch of medicine, particularly as the function of the family doctor is not yet clearly defined.

But the fact that we do not know these things need not inhibit the reform of undergraduate education at all. For the aim of this, now, is first and foremost to *educate*—i.e., to give the student *not* knowledge but the power to utilise knowledge.

That he must know facts is obvious, and that in his early days he cannot find these out for himself but must be given them is equally obvious. His and his teachers' primary purpose, however, must be that he learns how to learn for himself. Therefore the factual content of the undergraduate period does not have to be any particular percentage of the total of medical knowledge; it has to be chosen for its relevance to future learning, not for its relevance to future practice. Equally important, the student's progress must be assessed primarily on his ability to reason and utilise knowledge, and not merely in terms of the amount he knows. Similarly his clinical proficiency must be judged on the soundness of his method, of which the correctness of the physical signs he elicits from a patient in an examination is but one indication. By the same token, if it be true, as is sometimes claimed, that the newly qualified of today know more than their predecessors ever did, this does not mean that all is really well with medical education.

If the object of undergraduate education is achieved, then gaps in knowledge and inadequacy of technique will be made good in the postgraduate period. If the object of undergraduate education is not achieved, then such gaps will probably remain for ever, and he will be largely denied the mastery of new data and the critical evaluation of new treatment. Though specialisation has come to stay, there is nothing the least static about the size or form of any particular specialty. The future happiness and success of specialist and general practitioner alike depend on his ability to learn and on his knowledge of general principles.

The following should be our objectives:

1. The student must learn how to learn for himself.
2. He must acquire a scientific method of thought—i.e., the power to reason and think critically.
3. He must achieve competence in clinical method—i.e., the techniques of obtaining information from patients.
4. He must gain an understanding of the responsibilities of a professional person.

If these objectives are reached the student will inevitably have built up a foundation of knowledge, including empirical knowledge. He will also have built a foundation of clinical experience, as regards the diagnosis, treatment, and prevention of disease on the one hand and the nature of man on the other. The exact content of the foundations of knowledge and experience will vary, but during the years of his postgraduate training, each student will be able to fill in those gaps relevant to his own future practice.

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The undergraduate course of studies, thus freed from the need to include all or even any fixed percentage of knowledge and technique, can now, and must now, be based on considerations of the processes of learning.

This granted, it is at once evident that many different arrangements of studies have much to commend them in theory. Until they have been tried in practice, there can be no way of judging between them, and in any case the judgment can be no more than a clinical one. It is therefore idle to speak of the curriculum as though there is somewhere a correct arrangement which will be correct for every school and every student. The best curriculum for any particular school is that which enables it to make the best educational use of all its facilities and enables its students to progress through successive stages of learning, each with a clearly defined objective.

The number and sequence of stages, together with the purpose and content of each, will vary from school to school; but there are certain requirements which must be met in every stage everywhere:

1. Its purpose must be equally clear to both teachers and taught.
2. There must be deployed in it those incentives to study which are relevant to that purpose.
3. There must be built into it such forms of assessment of the student's progress as are appropriate to its content.

It goes without saying that other objectives, contrary incentives, and inappropriate tests should be excluded as rigidly as possible.

A course of studies of this kind cannot be made by a mere alteration of the timetable, even if this is done with educational objectives in mind. An entirely new attitude to teaching is required, and reform of the curriculum will be ineffectual unless there is also a reform of the method by which the curriculum is devised, applied, and constantly assessed. In my opinion this is no longer a matter of administration from the dean's office. There is required for each stage of the course a team of men who are responsible for it. They should represent all those departments most closely concerned with that stage, together with others whose advice could be helpful, even if they are not likely to teach in it themselves. For example, preclinical teachers should be concerned with the planning and assessment of predominantly clinical stages, and clinicians with the predominantly preclinical stages.

The team should, moreover, be representative of whole-time and part-time teachers, thus ensuring that the largest possible number of all kinds of teacher are closely involved in the educational effort. In this way cooperation can be achieved; for, instead of every department competing for what it feels is its rightful portion of the student's time, each becomes more concerned with what it has to contribute to the common purpose of each stage of the student's development. Furthermore, it is only when a teacher is able to appreciate the overall picture of that development that he can judge at what stage his own subject can make its best contribution. At present the resources of a special department are often squandered because students are routed through it too early or too late. Frequently also a student is able to attend a department for one period only, although it has something to offer him at several stages.

The effective planning, execution, and frequent assessment of every stage of a real course of studies is quite beyond the capabilities of any dean's staff or curriculum committee; but every school could muster a team for each stage. Each team would be working towards a comprehensible and realisable objective, and would be able to define the content of knowledge and practical experience, deploy relevant incentives, and devise appropriate forms of assessment. If integration of staff were ensured, the student would be helped to integrate his knowledge for himself without the aid of elaborate timetable innovations —and neither the autonomy of departments nor the freedom of individual teachers would be lost.

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I do not imagine that there will be anything very fanciful about the objectives of any stage, nor anything very intricate about its organisation. It is possible already to see the general outline in several schools, and I would imagine that our traditional respect for sound clinical method based on an uninterrupted introduction to it will result in most universities preferring not to bring clinical experience very far forward in the course. Indeed one would expect the first stage to continue to be one of the study of the normal, based on the old preclinical departments together with new ones, such as genetics. The preclinical departments already form a kind of stage committee in most schools, but the addition to it of clinical and other representatives would, without necessarily taking part in the teaching at all, go far to create that unity of purpose, common outlook, and single terminology at staff level, without which students' work will remain divided into preclinical and clinical.

Later stages must of course continue to be based upon existing firms and departments, but the great strength of these will be fully utilised if all concerned know what they are trying to do. For example, a stage devoted to practice of clinical method must obviously use general inpatient firms; but the teachers on these firms would not be left, as now, to try to grapple with all aspects of medicine, and would have instead agreed limited objectives together with a chance to assess their results. Nor would they have to contend and compete with synchronous courses of instruction, of which neither the content nor the purpose was known to them.

It is in the later part of the present clinical curriculum that confusion and dissipation of effort are now so marked, particularly in regard to the purposes of outpatient experience and the contribution of special departments. Order can be created again out of near-chaos by this simple process of organising stages of learning and experience by groups of teachers responsible for them.

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Our peculiar system of hospital staff structure has provided us with a teaching device in the firm, which ensures that a small number of students are closely attached to a teacher who is personally responsible for them and for the patients with whom they are concerned. The student is thus constantly reminded that the care of the individual patient is the yardstick by which everything else is measured. He is able to learn of the professional responsibilities of a doctor by the only possible method—observing the doctor fulfilling them. Above all, the welding together of his education and practical training is assisted by his being required to focus both his integrated knowledge and his practical skill upon the problems of his patients. He is enabled to acquire empirical knowledge and experience and at the same time be encouraged to learn scientific method because his teacher can set him this example, can excite his curiosity, and can guide him as an individual through his personal difficulties of learning.

It is small wonder that other countries are endeavouring to create for educational purposes this firm system which considerations of hospital practice developed here. Unfortunately with us it has been weakened by many factors which we have not tried to offset. The first of these is simply that the clinical teacher has not got the time which is required for the care of both his patients and his students. The second is that we have continued to think of the firm as an inpatient organisation.

I believe that part of the last clinical year should be devoted to a stage of learning by experience under supervision, and that this should be based on attachment, for at least four months to a general medical firm, primarily in the outpatient department but extending into the wards. In this students should be responsible for individual patients as they now are on the traditional inpatient firm. Student and patient together would visit the special departments as the patient's condition demanded, and both would return to the doctor responsible for both.

At this stage it should also be easy to extend the student's experiences outside the walls of the hospital, to give him an understanding of the patient as a whole, and demonstrate the relation of medicine to the community. It is here that I would incorporate the general practitioner into the undergraduate teaching team, with membership of the committee responsible for this stage, so that he is conversant with the objectives which the student has been set and with the lines on which his development is planned.

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The provision of a new curriculum and a new type of administration, however, will not completely solve the problem of readapting medical education to present conditions of medicine. The inclusion into undergraduate medical schools of all that is meant by university education is also necessary. An essential requirement of this is interest in the individual student, so that he may develop in a stimulating intellectual atmosphere, with the encouragement and guidance of his teachers. It would be idle to pretend that this is now possible in all our schools.

If the medical student is to be a university student, then he must be treated as such, and the medical school must provide not merely teachers, a curriculum of classes, and an administration, but also an educational service. It is not enough to have a tutorial system which is a mere adjunct to the other forms of teaching. The system providing encouragement and guidance must not be separate from the system of reproof, which is represented by authority and vested in the dean. Any dichotomy can only result in resentment of authority or frustration of encouragement. But if all good incentives are mobilised and coordinated into one discipline, then progressive assessment of the individual becomes possible, and he can be given such help as he is known to need. The medical school must have some kind of director of studies as well as a dean—just as our older university colleges have a senior tutor as well as a master—tutors and supervisors as well as teachers.

The increased need for education requires also a new attitude to halls of residence. In many universities these have long been recognised as a means whereby students can educate themselves by indirect contact with several faculties. In his later years, however, the medical student

lingers on after his colleagues in other disciplines and tends to become more attached to a hospital than a university. Those who have no home in the vicinity may live in a hostel belonging to the medical school, but such hostels, as their name implies, are often thought of as merely lodging-houses conveniently near the wards. There is a great need for a change of attitude so that these places can play their full part in education. All students should spend some time in them, and not merely those who have difficulty in finding accommodation elsewhere. Far greater responsibility for the corporate life of the student body should then be given to the students themselves—a necessary experience for those who are going to carry heavy professional burdens but who now tend to be kept from both responsibility and community life up to the age of 24. In this field also the teaching staff have a large part to play, not as persons of authority or with administrative duties, but as senior members of a single professional and intellectual community.

In none of these things, which I believe to be so important, do I envisage any kind of spoon-feeding or wet-nursing of students. On the contrary, I am advocating that they be regarded much less as groups of overgrown schoolboys, and much more as individual adult members of a profession. Their reactions to the education offered must be regularly sought, as in most other countries it now is; and they should feel free to seek advice on problems of learning without fear of jeopardising their careers. In the past medical schools have been so concerned with teaching and examinations, that few facilities, either material or in personnel, now exist for education. The need for them is urgent, and they are required for the postgraduate as well as the undergraduate. The days have passed when any medical school can feel that its responsibility for a man has ended when he has passed his final examinations.

" Finals ", of course, are now a misnomer; for they merely indicate a qualification which is necessary before the student is in his last year of general internship, legally able to undertake the responsible practice under supervision of which this stage of experience is composed. It remains to be seen whether this stage should be increased in duration or advanced in time. But it is already a responsibility of the medical schools, though not one which they have been able fully to discharge. They will need to develop a much more active system of caring for the individual before they can do so.

It will only be when such a system has developed that many other features of a university education in medicine can be properly undertaken. For example electives, and opportunities for students to study a subject in depth by undertaking some piece of original work, depend for their full effect on adequate knowledge and guidance of the individual. Furthermore we have to regain in this country greater freedom for each student to develop in his own way and at his own speed. We have had an overcrowded curriculum for so long, that we have almost come at accept the idea of having the same timetable for every student. Worse still, the system of grants, by which most students are financed, has encouraged the idea, in both medical schools and grant-giving authorities, that there is a fixed maximum duration of studies which is properly common to all students. This is most unfortunate, because no-one has ever laid down more than a minimum period, and students do not all progress at the same speed. It is an odd paradox that by so rightly removing financial barriers to medical education in this country, we have at the same time removed from the individual his necessary freedom to vary from the average. In the United States where most students are privately financed, it is easier for a man to step off the production-line than it is here, where courses are repeated only by students who have done badly. In Sweden, where students can get State loans but not grants, the finishing line is an entirely personal affair. Our system of a class of students all taking their examination on the same day is regarded as most unusual.

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In my view readaptation of medical education depends then, on (1) a course of studies, based on stages of learning together with relevant forms of assessment; (2) a more effective method of operating and maintaining the new curriculum, and (3) a university atmosphere. If these three things are provided, then undoubtedly new teaching techniques will emerge; or at all events we shall learn much more than we now know about the problems of education and the answers to them. In order to set our house in order, however, we do not need any more information than we now have. It is as useless as it is dangerous to wait for scientific proof that this or that is necessary, or that one scheme is better than another. This is a matter for clinical judgment. It is futile, and really only a form of escapism, to wait for some magic concrete plan which can be put into administrative effect and then forgotten.

The main obstacle to the full implementation of these three things is that very few teachers have enough time in which to give undivided attention to education. This can be remedied only by ensuring that part-time clinical teachers particularly, have enough sessions at the teaching hospital to enable them to practise clinical medicine, educate students, and engage in research. It is essential that this is done, if the country is to continue to have a high standard of medical service. It will inevitably cost money, but medical education is important. It alone can pass the advances of medicine on into effective practice. It is hopeless and wasteful to tackle it half heartedly, and the most economical medical school, like the most economical hospital, is the one which sets out to be the best rather than the cheapest.

If in the National Health Service we can but make the terms and conditions of service of medical teachers relevant to the demands of education, we shall be able to mobilise a quite remarkable number of assets. Indeed, we should be in a far better position than any other country to solve the remaining problems of medical education.

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It seems justifiable to expect, therefore, that after a long period of difficulty, we can now enter a period in which medical education will be once more in equilibrium with medicine. Certainly we should be able most successfully to give an education in medicine while retaining and even improving our ability to teach sound clinical method. But this does not mean that we will then be automatically giving a good preparation for medicine as a profession.

The basis of British practice is that each patient, whether in his home or at hospital, has one doctor who takes personal responsibility for him; but there is no doubt that this basis has been weakened, and that too often there is uncertainty as to who is really responsible for the patient. The doctor also has a responsibility to the community, which cannot be discharged merely by attending to individuals; and students have to be made aware of very

many important duties of the profession other than that of diagnosing and treating disease. Lastly we have, always, the problem of the way in which we discharge our duties—the standard which the profession sets for itself and the nature of its corporate discipline.

In times of great change the standards of a profession are at risk, and all ethics have to be translated into new terms. Moral exhortation without content or direction is a futile thing, and today the student must be brought to share the problems which face his teacher both as concern the patient and the profession. He must learn that science, which he must use, searches only after truth and has no humanitarian ends in view; but he must also learn that in a *professional* community, unlike others, how a decision is made is more important than what is decided.

These problems are difficult—but only because medicine and the profession face a greater challenge than ever before. I would say that there has never been a better time than this in which to be a doctor: the opportunities, like the challenge, are greater than ever before. They are greater, I believe, in this country than in any other: we are in a better position to solve all our problems. But we cannot do so unless we set our sights high. We must accept that in a time of change the most idealistic approach is the most realistic. The pursuit of quality is the only aim proper to our profession and the only one it can afford to have.

THE EFFECT OF TEST FEEDS ON THE PLASMA LIPIDS

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IT has been shown repeatedly that the type of fat in the diet affects the lipid content of the plasma. But the kind of investigation so far reported has several disadvantages.

The lipid changes have been produced by feeding particular oils and fats for several days, weeks, or even months, with the remainder of the diet under careful control; and in these circumstances several weeks elapse before the plasma lipids reach a constant level on the basal diet and again with each fat under test. Because during all this time the basal diet has to be rigidly controlled (Ahrens et al. 1957), many investigators have resorted to giving this diet as homogenised liquid feeds (Kinsell et al. 1953). Apart from the practical difficulties—especially for studies on normal people and outpatients—arising from long-continued control, the test materials may not be available in sufficient quantity, or may be unsuitable for long-term administration (e.g., tung oil). Moreover the effects of trace materials, and the relative importance of particular substances, are often difficult to evaluate when whole diets are being fed.

Hence, for identifying and defining the dietary factors that influence human lipid metabolism, there is need of a quick and reproducible biological test. This should last no more than 12 hours; for then only the test substance need be fed, the experimental conditions can be easily controlled, and any lipid changes can be compared with the effects of fasting for an equal period. Also, if the test is to be used as a method of biological assay, it should evoke reproducible responses in normal people and be sensitive to small changes.

Such a method, in this laboratory, has been in use for 4 years. Single test feeds of oils are given under standard conditions so that the effect of each oil on the plasma lipids can be quickly and clearly demonstrated. In this paper we illustrate the method first by describing the effect of arachis oil on the plasma glyceride, phospholipid, and cholesterol, and then by reporting the effects of various other oils.

Materials and Methods

The subjects were healthy male medical students (aged 19–33) on the same kind of diet and activity. They were not allowed dietary fat during the 12 hours before the experiment nor excessive fat on the previous day, and their fasting plasma was clear. A light breakfast of fat-free drinks, dry toast, and marmalade was allowed 2-3 hours before the experiment.

The Test Feed

50 g. of the oil is given as a single feed, emulsified with 50 ml. of skimmed milk and 50–100 ml. of tap water, and flavoured if desired. (With feeds of less than 30 g. the changes in the plasma lipids are small and inconsistent, while feeds above 60–70 g. often cause nausea without proportionately increasing the plasma-lipid changes.) The emulsions must not be oily or thick and should be at room temperature; they should be drunk quickly, without breathing through the nose. The feeds are followed immediately by a strong-tasting drink, such as blackcurrant cordial, and by an apple.

A standard procedure without unpleasantness is essential; for, if the subjects are nauseated, the absorption of the feed is apparently delayed and the plasma-lipid changes are prolonged and inconsistent.

Collection of Blood Samples

Samples were taken before the feeds, and at $1^1/_2$, $3^1/_2$, $5^1/_2$, 7–9, and 24 hours after them. The blood was obtained by venepuncture using siliconed syringes and run into 3·8% sodium-citrate solution buffered to pH 7·4 (18 ml. of blood to 2 ml. citrate solution); the plasma was separated immediately by centrifuging and then stored at 4°C. The analyses were begun next day.

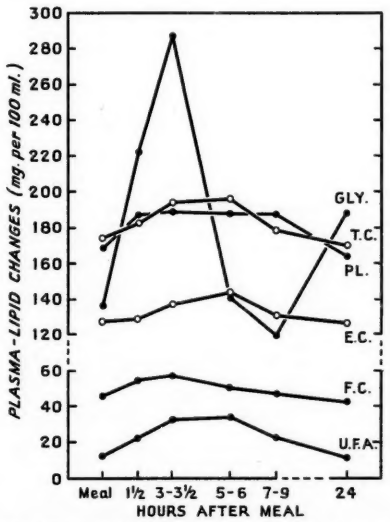

Fig. 1—The plasma-lipid levels before and after the 50 g. meals of arachis oil (mean of six results).

GLY., glycerides; T.C., total cholesterol; PL., phospholipids; E.C., esterified cholesterol; F.C., free cholesterol; U.F.A., unsaturated fatty acids.

Methods of Analysis

Lipid phosphorus was determined by the method of Fiske and Subbarow (Hawk et al. 1947), total and free cholesterol by that of MacIntyre and Ralston (1954), unesterified fatty acids according to Grossman et al. (1954), and plasma total esterified fatty acids by the method of Morgan and Kingsbury (1959).

The entire series of plasma samples from each individual, plus the various standards, were analysed together in triplicate. In this way fine differences between samples could be recognised. The coefficient of variation of replicate samples by each method has always been less than 0·8%. Total-cholesterol or phospholipid changes of more than 3 mg. per 100 ml. between the samples of one run, have therefore been accepted as significant.

Effects of Arachis Oil

After single feeds of 50 g. arachis oil the first observed change in the plasma lipids was an increase of glycerides, which reached a maximum 3–3$^1/_2$ hours after the feeds, after which the values fell rapidly for 3 hours and then more slowly and variably. This increase in glycerides was accompanied by a slower rise and fall of the plasma cholesterol, phospholipids, and unesterified fatty acids, which reached their maximum at 3–6 hours after the meals, decreased gradually in the next 3 hours, and then fell very slowly. The amount and the timing of the cholesterol and phospholipid changes were very similar. The behaviour of the plasma lipids is shown in fig. 1, which gives the average values obtained in six volunteers.

It has been found that if too little of the oil is absorbed, or if the oil is absorbed too slowly, the subsequent changes in the cholesterol and phospholipids are inconsistent and unpredictable. Adequate absorption of the oil, normally timed, is therefore a necessary condition of the experiment; and we do not consider it adequate unless the plasma glycerides rise between the fasting and 3$^1/_2$-hour samples and fall between the 3$^1/_2$-hour and 5$^1/_2$-hour samples. Thus, if the plasma glycerides had not increased by more than 60 mg. per 100 ml. plasma (0·7 mMol. per litre) at 3$^1/_2$ hours, and if over a third of this increase had not been removed by 5$^1/_2$ hours, the experiment was rejected. The glyceride increases shown in our results represent, therefore, the differences between the fasting and 3$^1/_2$ hour samples; and the percentage clearances are the percentage removal of these increases between 3$^1/_2$ hours and 5$^1/_2$ hours.

In normal subjects with a clear fasting plasma and a

CHANGES IN PLASMA-LIPID LEVELS CAUSED BY SINGLE FEEDS OF VARIOUS OILS

Type and number of feeds	Plasma-lipid changes (mg. per 100 ml.) average and range									Fig. 2 no.	Iodine value of oil
	Glycerides		PL.	T.C.	F.C.	E.C.	T.C./PL.	F.C./E.C.	U.F.A.		
	Increase	Decrease									
Group 1: Coconut (6)	144 (106–257)	46% (38–62)	23 (20–25)	27 (24–29)	11 (9–12)	16 (15–17)	1·12 (0·96–1·4)	0·69 0·53–0·80	17 (14–24)	1	8
Palm (4) ..	134 (64–182)	52% (48–65)	20 (18–24)	21 (18–24)	8 (5–10)	13 (10–15)	1·05 (0·80–1·2)	0·61 (0·40–0·66)	16 (15–19)	2 2	52
Arachis (18)	143 (81–210)	57% (51–65)	20 (16–26)	20 (16–24)	7 (5–8)	13 (12–15)	1·00 (0·84–1·20)	0·54 (0·33–0·58)	20 (14–28)	3	89
Olive (6) ..	179 (123–234)	50% (42–56)	21 (19–24)	19 (18–22)	6 (5–9)	13 (12–15)	0·91 (0·85–1·1)	0·46 (0·38–0·59)	19 (15–26)	4	83
Tung (2) ..	90 (64–116)	42% (38–49)	17 (14–21)	18 (15–22)	5 (4–6)	13 (11–6)	1·1 (1·1)	0·38 (0·38–0·37)	14 (13–14)	5	165
Group 2: Sunflower (5)	172 (110–197)	63% (49–72)	12 (10–14)	7 (6–8)	2 (2–3)	5 (4–7)	0·58 (0·56–0·68)	0·4 (0·36–0·68)	24 (19–31)	6	131
Safflower (3)	146 (92–216)	48% (41–53)	13 (9–16)	6 (5–8)	2 (2–3)	4 (3–6)	0·52 (0·5–0·55)	0·50 (0·33–0·66)	19 (12–28)	7	138
Corn (4) ..	138 (103–157)	51% (41–62)	14 (11–15)	6 (4–8)	2 (2–3)	4 (3–5)	0·43 (0·4–0·65)	0·50 (0·4–0·7)	21 (19–26)	8	113
Soya (2) ..	118 (122–114)	44% (36–52)	14 (14–15)	8 (7–9)	3 (3)	5 (4–6)	0·57 (0·5–0·6	0·60 (0·5–0·75)	21 (17–25)	9	134
Cotton-seed (2) ..	141 (112–170)	48% (40–51)	14 (14–15)	9 (9–10)	3 (3)	6 (6–7)	0·66 (0·6–0·7)	0·50 (0·4–0·6)	16 (17–15)	10	106
Whale (6) ..	166 (100–158)	68% (53–79)	14 (12–16)	6 (4–8)	2 (1–3)	4 (3–5)	0·48 (0·4–0·58)	0·5 (0·36–0·64)	21 (11–28)	11	128
Pilchard (3)..	125 (106–139)	53% (38–67)	15 (12–17)	8 (7–10)	3 (3–4)	5 (3–7)	0·54 (0·47–0·57)	0·6 (0·5–0·6)	15 (13–23)	12	152
Heated tobacco-seed (12)	160 (64–256)	56% (45–59)	10 (5–15)	5 (2–10)	1 (0–3)	4 (2–8)	0·50 (0·21–0·57)	0·25 (0·0–0·6)	20 (12–26)	13	136
Group 3: Stored crude tobacco-seed (12)	145 (99–204)	61% (43–67)	10 (5–13)	2·0 (0–6)	−3·0 (−1–−6)	5·0 (2–10)	0·20 (0–0·7)	−0·6 (−1·2–−0·2)	19 (13–24)	14	136
Crude tobacco-seed (12)	188 (72–470)	62% (49–78)	0·25 −5–+5	1 (−3–+3)	−8·0 (−3–20)	9 (+3–+20)	4·0 (−0·75–+2·0)	−0·9 (−0·8–−1·1)	19 (12–39)	15	136
Fasting (12)	−24 (+1–−68)		−5 (−2–−10)	−6 (−1–18)	−3 (−2–−4)	−3 (−1–−9)	1·2 (−0·66–+3·0)	1·0 (+0·2–+3·0)	−3 (+3–10)	Not included in Fig. 3	..
Fraction A (2)	123 (116–130)	48% (39–57)	9 (7–11)	2 (0–4)	−2 (−1–−3)	4 (1–7)	0·2 (0–+0·3)	−0·5 (−1·0–0·4)	16 (15–18)		..
Fraction B (2)	161 (135–177)	56% (47–65)	12·0 (9–15)	7 (6–7)	2·0 (1–3)	5 (5–4)	0·58 (0·66–0·47)	0·4 (0·2–0·75)	25 (16–34)		..
Cod-liver (2)	101 (19–113)	62% (48–76)	13 (11–15)	8 (5–11)	3 (2–4)	5 (3–7)	0·61 (0·45–0·73)	0·6 (0·7–0·57)	30 (21–39)		150

PL. = Phospholipids. T.C. = Total cholesterol. F.C. = Free cholesterol. E.C. = Esterified cholesterol. U.F.A. = Unsaturated fatty acids.

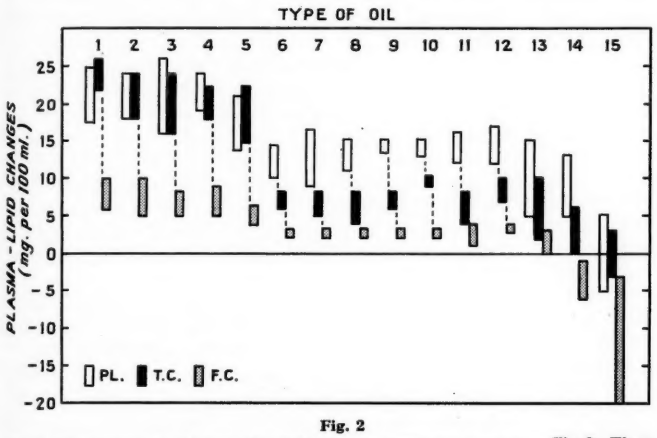

Fig. 2

Fig. 2—The changes in plasma phospholipid and cholesterol caused by the various oils (numbered as in table).

The effects of fractions A and B, cod-liver oil, and of fasting, shown in the table are, for the sake of simplicity, not included in the figure.

PL.=phospholipids; T.C.=total cholesterol; F.C.=free cholesterol.

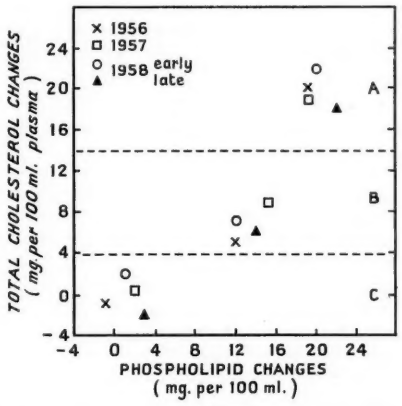

Fig. 3

Fig. 3—The response of three subjects to the same test feed when fed at intervals over 3 years.

A, arachis; B, heated tobacco-seed oil; C, crude tobacco-seed oil. The fasting plasma levels of the three subjects were: A, phospholipids 98 mg. per 100 ml., total cholesterol 235 mg.; B, phospholipids 158 mg., total cholesterol 169 mg.; C, phospholipids 222 mg., total cholesterol 254 mg.

normal absorption of glyceride, plasma cholesterol and phospholipid reached their maximum 3–6 hours after the feed. The changes in phospholipids and cholesterol caused by the feeds can be expressed by the values:

$$\frac{(3\frac{1}{2}\text{ hour}-\text{fasting})+(5\frac{1}{2}\text{ hour}-\text{fasting})}{2}$$

The figure obtained in this way we call the lipid response.

Effects of Various Other Oils

Single 50 g. feeds of other oils were fed in the same way to normal volunteers. The oils used, the number of experiments, and the lipid response are shown in the table.

Non-polymerised refined tung oil was supplied by Unilever Co. The other oils were of edible grade and obtained from Unilever Co., H. M. Faure & Co., British Cod Liver Oils Ltd., and through Hess Products and Cyclo Chemicals Ltd.

"Stored tobacco-seed oil" is crude oil which has been stored at 4°C in the dark for 9 months and "heated tobacco-seed oil" is the crude oil heated by steam to 165°C under a high vacuum.

"Fraction A" and "fraction B" were prepared from the fatty acids obtained by dehydrating ricinoleic acid. Those liquid below 10°C (Hilditch 1956) were stored at 0°C for several weeks in the dark in an atmosphere of nitrogen; a solid fraction was separated by filtration at 0°C. Both liquid and soil fractions were then frozen at 20°C, stored at 0°C for several weeks, and filtered as before. The fractions solid at 0°C were combined and called fraction A; the combined fractions were called fraction C. They were fed as ethyl esters.

With all the oils, plasma glyceride rose by more than 60 mg. per 100 ml. and over a third of this increase was removed at $3\frac{1}{2}$–$5\frac{1}{2}$ hours. But the different oils produced three different types of lipid response, and can accordingly be placed in three groups (table and fig. 2):

Group 1.—These raised the total-cholesterol and phospholipid levels by about 20 mg. per 100 ml., without altering the ratios of total cholesterol to phospholipid or of free cholesterol to esterified cholesterol.

Group 2.—The increases in total cholesterol and phospholipid were smaller, but the ratio of total cholesterol to phospholipid was reduced. The ratio of free cholesterol to esterified cholesterol was unaltered.

Group 3.—With the oils in this group (crude and stored tobacco-seed oil) the levels of phospholipid and total cholesterol *rose* only very slightly, or actually *fell.* The level of free cholesterol consistently fell, but both the phospholipid and the free-cholesterol/esterified-cholesterol ratios were variable.

These different lipid responses were not associated with differences in the amounts of glyceride increase.

In control experiments a fat-free diet, taken for 24 hours, reduced the levels of all the plasma lipids estimated.

Reproducibility of Lipid Response

Fig. 3 shows the changes in cholesterol and phospholipid levels obtained with oils of the three groups. Each volunteer received one oil four times, and on each occasion it produced the same kind of response, distinct from the effects of the other oils. In the experiment recorded in fig. 4, each of four volunteers took three different oils. All four subjects showed the same type of lipid response to a given oil, and similar alterations in response when the oils were changed. (In fig. 4, for simplicity, only the cholesterol changes are shown.)

Thus healthy people gave the same lipid response to a particular type of oil, even when the tests were separated

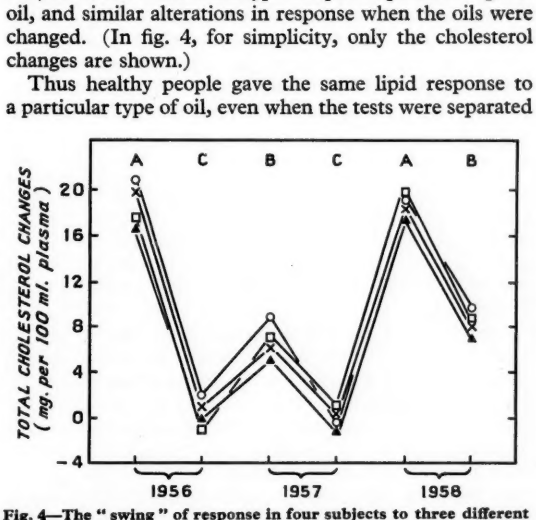

Fig. 4—The "swing" of response in four subjects to three different types of oil (A, arachis; B, heated tobacco-seed oil; C, crude tobacco-seed oil).

The fasting levels of total cholesterol in the four subjects were: ×, 181 mg. per 100 ml.; □, 211 mg.; ○, 183 mg.; ▲, 189 mg.

by a year; and, by changing the oil, the volunteers could be " swung " to another response. Clearly, the reproducibility of the results was not due to insensitiveness of the test. This could in fact distinguish between the effects not only of different oils but even of the same oil before and after treatment by heat (table and fig. 2).

Discussion

As a method of biological assay, the test feed has the advantage of simplicity, speed, and ease of control, and it enables us to ascertain the effects of single substances, using comparatively little material. Their effects on plasma lipids are demonstrated not only (as in the longer experiments) by the changes in cholesterol and phospholipid but also by the relation of these lipids to one another and the relation of free cholesterol to esterified cholesterol. The alterations in these relations are new findings which suggest that plasma-phospholipid and plasma-cholesterol levels are under separate physiological control. Even in normal people the phospholipid/cholesterol ratio is not necessarily constant, and its different behaviour in response to group-1 and group-2 oils raises the interesting question whether it is ordinarily set by the diet.

The different effects of crude and heated tobacco-seed oils is a further new finding, which will be discussed elsewhere. The difference does not seem to be due to alterations in the fatty-acid composition of the oils.

It is difficult to compare our results with those of other workers who have used single feeds for studying changes in the plasma lipids (Man and Gildea 1932, Lindholm 1956, Dole et al. 1959); for, although Man and Gildea, for example, recorded similar phospholipid changes, their aim was to see whether lipid changes did in fact occur, and not to create a standard method of biological assay (Kingsbury 1958). Reasons why our findings may differ from those of the longer (more usual) experiments are numerous:

1. The oils may have been subjected to different treatment (compare our different results with crude and heated tobacco-seed oils).

2. Most of the other work has been done on patients, whereas ours was on normal subjects.

3. The results reported here concern only the period of lipid increase immediately following the fatty meals, whereas the results of long-term experiments must be the algebraic sum of varying lipid absorption, plasma-lipid increases, and clearance of lipids from the blood.

4. The two methods may be sensitive to different variables.

5. Whereas our results describe changes from a standard basal condition, the changes in the long-term experiments result from altering one diet for another. This point can be illustrated by the fact that in the long experiments corn oil has so often caused an immediate and progressive fall in the plasma-cholesterol level, whereas in our experiments it caused a rise.

It is all the more interesting, therefore, that our results should in many ways resemble those of Ahrens (1957), using the longer method. In both investigations oils having iodine values above 100 produced low levels of plasma cholesterol, whereas with oils which have iodine values below 90 the cholesterol level increased with the saturation of the fat (see table). Whale, pilchard, and cod-liver-oil—which are rich in polyunsaturated acids but not in those essential for the normal health of animals (Thomasson 1953)—gave the same kinds of lipid responses as the edible vegetable oils (corn, soya, sunflower) whose high content of unsaturated acids is composed mainly of " essential " fatty acids. This is similar to the results of Ahrens (1959).

In view of the similar effect of fish oils and vegetable oils on the plasma-cholesterol, it is interesting to reflect that, though an increase of tri-unsaturated acids in the tissue lipids of animals is strong evidence for a deficiency of the essential fatty acids (Jorgensen and Holman 1958), this accumulation of trienes has been reversed by cod-liver oil (Rieckenhoff et al. 1949, Dam et al. 1959), and that though this oil is rich in polyunsaturated acids, it has a very low essential-fatty-acid activity when assessed conventionally in terms of a normal skin in animals. Thus it seems that many of the polyunsaturated acids, such as those found in cod-liver oil, may not only lower the blood-cholesterol level but also correct fatty-acid deficiencies.

As conventionally defined, a " non-essential " acid very similar in physical properties to the " essential " linoleic acid is its *cis-trans* isomer, which has a melting-point of about $-3°C$ (Privett et al. 1955) or up to 7°C (Jackson et al. 1952). Unfortunately it cannot yet be made in quantities sufficient for feeding experiments; but, as an alternative, we hoped to obtain low-melting-point isomers of linoleic acid from dehydrated ricinoleic acids (Hilditch 1956). Ultraviolet spectroscopic analysis (Hilditch et al. 1951) of our fractions A and B showed that about 60% were linoleic acid or its isomers, of which about half were conjugated; probably the *cis-trans* isomers were concentrated in fraction B (melting-point 0–10°C). As both these fractions raised the plasma lipids only slightly (see table) it appeared that the lipid response to the natural *cis-cis* linoleic acid (approximately 70% of tobacco-seed oil) was neither prevented nor obscured by its conjugated or other isomers.

Our results with tung oil are not at present explainable. Sinclair (1959) has suggested that it should have the same effects as other non-essential oils of equal unsaturation; but this ignores its undoubtedly different properties, as evident in its chemical reactivity, rate of oxidation, and absorption spectra in the ultraviolet. Possibly the biological action of conjugated fatty acids of this type differs from that of non-conjugated acids of equal unsaturation.

The reasons for the different effects of the various oils are not yet established, but we cannot see why many factors in oils should not act in different ways. For instance, the amount of the biologically essential linoleic acid usually given as a dietary supplement is about 50 g. a day (Olson et al. 1958). This would be about 5–10% of the total dry weight of the daily diet of our volunteers and probably about 10% of a patient's hospital diet. In animals, however, severe essential-fatty-acid deficiency can be corrected by less than 0·5% of linoleic or arachidonic acid in the diet (Holman 1950)—an amount of arachidonic acid which is said to have no effect on the plasma lipids of man (Keys et al. 1959). It may be that, in large amounts, unsaturated acids (both essential and non-essential) alter the physicochemical properties and hence the metabolism of their esters (glycerides, cholesterols, phospholipids, &c.) (Klein and Martin 1959). This need not exclude a simultaneous correction of any existing fatty-acid deficiency (Fulco and Mead 1959).

In addition, an effect from the non-saponifiable or trace components of an oil cannot be excluded; and this may be the reason why crude tobacco-seed oil and heated tobacco-seed oil (though we have found no difference in their fatty-acid composition) have different effects.

Summary and Conclusions

A method for the biological assay of dietary lipids is described in which changes in the plasma glycerides, cholesterol, and phospholipids are measured after single 50 g. feeds of the fat under investigation. Plasma samples are collected before and $1^1/_2$, $3^1/_2$, $5^1/_2$, 7–9, and 24 hours after the test feed.

The conditions for success are a period of fat deprivation and a clear fasting plasma before the experiment; a standard method of feeding; the avoidance of nausea; and adequate absorption of the oil. The criterion of adequate absorption is a rise in plasma glycerides by more than 60 mg. at $3^1/_2$ hours, of which increase over a third must have been removed by $5^1/_2$ hours.

The plasma-cholesterol and plasma-phospholipid changes produced by the feeds are called the lipid response. This response differs with different oils, the characteristic changes being reproducible both in different subjects and in the same subjects after long intervals.

The method has the advantage of needing only small amounts of material, of being quick and sensitive, of easily allowing experimental controls, and of not requiring special diets.

It is not offered as an alternative to long-term experiment, but as a supplementary method especially useful for rapid biological assays.

New contributions by this method are (1) the finding that different oils have different effects on the plasma phospholipid/cholesterol ratios, (2) the use of these changing ratios to classify the type of lipid response to the experimental fat, and (3) the different effects of crude and heated oils.

The reasons for the different effects of the various oils are not known, but they are unlikely to be all due to one type of substance or property.

We wish to thank the volunteers, without whom the work would have been impossible and who received no recompense for much unpleasantness; Mr. W. Darrel and Mr. P. A. Dupont for technical assistance; Prof. C. G. Rob and Mr. R. W. Best (Unilever Ltd.) for advice and interest, and Bush & Co. for generous gifts of flavourings. Part of this work was included by K. J. K. in a thesis for the degree of doctor of philosophy, London University, 1958.

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MYOCARDIAL INFARCTION AMONG MEMBERS OF COMMUNAL SETTLEMENTS IN ISRAEL

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THE incidence of ischæmic heart-disease differs strikingly between different countries (World Health Organisation 1956) and even in a single country between different ethnic and social groups (Brock and Bronte Stewart 1955, Brunner and Löbl 1957, 1958, Dreyfuss 1953, Toor et al. 1957).

We have sought to examine the influence of physical exercise on the incidence of myocardial infarction in the Kibbutzim and Kvutzoth. These are communal settlements in Israel, whose members are ethnically homogeneous and where the environmental conditions (standard of living, diet, housing, cultural activity, and recreation) are virtually uniform. No difference is made between teachers, clerks, businessmen, local political leaders, drivers, fishermen, masons, and agricultural workers.

Material and Methods

This survey covers the incidence of myocardial infarction in the ten years up to Dec. 31, 1959, in 8500 people (4500 men and 4000 women) who at the end of 1949 were aged 30–55.

One of us (G. M.) visited each of the 58 settlements in which these people lived. Because of the comprehensive medical service in these settlements, we had no difficulty in obtaining data on all fatal cases (sickness certificates, hospital case-records, postmortem reports, and electrocardiograms) and surviving patients who had had myocardial infarcts (detailed clinical examination and electrocardiograms). All patients except 2 were admitted to hospital soon after the infarction. Thus the diagnosis of myocardial infarction, whether the patient survived or died, was based on the clinical picture and on an unequivocal electrocardiographical diagnosis. As electrocardiographic proof of myocardial infarction we accepted only typical Q waves or typical T waves, or both together. Not included in this review are patients who presented the clinical picture of angina pectoris with or without the electrocardiographic pattern of coronary insufficiency.

Findings

In the ten-year period there occurred, among the population of 8500, 111 cases of myocardial infarction; 34 patients died and 77 survived. Of the 4000 women, only 9 had infarction; and of these 2 died and 7 survived.

In the communal settlements of all persons in the age-group of the sample, 30% are engaged in sedentary work and 70% in non-sedentary work. By contrast, in the cases of myocardial infarction, of the 34 who died 19 were engaged in sedentary work; and, of the 77 who survived, 42 were engaged in sedentary work. The group of non-sedentary workers included also those doing very light bodily work, such as that of confectioner or light physical work in industrial factories. When classifying the men according to their occupation, we took into account work done by the patient for at least four years before the attack. Particular care was taken not to include in this or any other group men who had changed their occupation as a result of their illness.

For non-sedentary male workers the annual incidence was 1·36 per 1000; whereas for sedentary male workers the annual incidence was 4·1 per 1000. Thus the incidence was three times greater in the sedentary workers. The

mortality-rate was likewise three times greater in this group.

Comment

These data support those of Morris (Morris et al. 1953, Morris and Crawford 1958) indicating the preventive influence of bodily activity.

Jewish people are reputedly especially prone to ischæmic heart-disease (Epstein et al. 1957); but our findings do not support this belief. The annual incidence of myocardial infarction among the sedentary Jewish workers whom we studied is almost identical with that in London sedentary workers observed by Morris et al. (1953). On the other hand, the incidence of myocardial infarction among non-sedentary workers in Kibbutz (0·8 per 1000 men per year) is only half the incidence among London postmen who walked in their daily work (1·6 per 1000 men per year).

These findings underline the importance of physical exercise as a factor in the prevention of myocardial infarction.

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INVOLUTIONARY SCLEROSIS AND DIASTOLIC HYPERTENSION

EFFECT OF ENVIRONMENTAL CHANGE

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INDIRECT evidence, based on hospital statistics, has shown that arteriosclerotic cardiovascular disease is more common among the Yemenite community who have lived in Israel for a long time than among new immigrants from Yemen (Dreyfuss 1953, Toor et al. 1960). The blood-cholesterol and blood-phospholipids are higher among Yemenites settled in Israel than among new immigrants from Yemen (Toor et al. 1954, Brunner et al. 1955). It was shown by one of us that there is practically no diabetes mellitus among new immigrants from Yemen, while among those settled in Israel for more than twenty-five years, its prevalence is comparable to that among Jews from the western world (Cohen 1960).

The purpose of our investigation was to determine whether the difference in environment between Yemen and Israel also affects the prevalence of involutionary sclerosis and diastolic hypertension among these contrasting groups. Yemenite Jews form particularly suitable material for this study, being a homogeneous group with little or no intermarriage with other groups. Constitutional factors, therefore, cannot affect the clinical differences between the settled and the new immigrant groups.

In order to have the groups unselected, the entire Yemenite population above the age of 30 in chosen areas were visited in their homes. The diagnosis of diastolic hypertension was based on manometric examination, and that of involutionary sclerosis on ophthalmoscopic examination of the retinal vessels. This procedure seems to be as reliable as any one method for the diagnosis of involutionary sclerosis, and is probably the most suitable for a house-to-house examination. It is, however, appreciated that changes in the retinal blood-vessels do not necessarily indicate changes in the entire vascular tree, nor does the absence of any change rule out the possibility of arteriosclerosis in other parts of the body.

Material and Methods

The survey was carried out during 1959. The first group, the "new immigrants", consisted of the entire population, over the age of 30, in two settlements near Jerusalem, Yishi and Noham. They had all immigrated from the Yemen within the past ten years. The group contained 147 persons, 70 men and 77 women. The second, the "settled" group, consisted of the entire population, over the age of 30, in two Jerusalem quarters, Nahalat Ahim and Mishkenot. They all had lived in Israel for over twenty-five years, and some were born there. This group contained 125 persons, 55 men and 70 women. All examinations were carried out at their homes. Age, sex, and time of arrival to this country were noted. A short physical examination was carried out in each case. Resting blood-pressure was taken several times. Urine was examined for albumin with sulphosalicylic acid, and for glucose with glucose reductase ('Test Tape', Lilly).

Diastolic hypertension was considered to be present when the systolic pressure exceeded 140–150 mm. Hg, and the diastolic 90 mm. Hg. The criteria for involutionary sclerosis were: (*a*) narrow retinal arteries, (*b*) unusually straight course of these vessels, and (*c*) narrowness of their bifurcations. Many of these cases showed slight variations in calibre of the arteries, and some changes at the ateriovenous crossings. These were not, however, thought to be essential for the diagnosis of involutionary sclerosis. The arteries were considered to

TABLE I—AGE (YEARS) AND SEX-DISTRIBUTION IN THE TWO GROUPS

—	30–55 years				Over 55 years				Total	
	M		F		M		F		M	F
	Number of patients	Average age	Number of patients	Average age	Number of patients	Average age	Number of patients	Average age		
New ..	44	40·0 ± 7·8*	59	41·5 ± 7·3	26	69·2 ± 7·0	18	67·1 ± 8·0	70	77
Settled ..	30	40·7 ± 7·5	36	41·9 ± 8·3	25	68·1 ± 6·9	34	66·2 ± 7·1	55	70

* Standard deviation of the mean.

be narrow and straight if at least 2 out of the main 4 vessels in each fundus were found to be affected, and the bifurcations were considered narrow if the majority of them were affected. There is a certain subjective element in the diagnosis of involutionary sclerosis in the retina, and therefore only cases where there was no doubt of the retinal diagnosis were included. 60% of all cases of involutionary sclerosis showed systolic hypertension. Fisher's exact method for a 2×2 contingency table was used for statistical analysis.

Results

Table I shows the average age in each age-group for men and women is almost the same in the " settled " and " new immigrants " groups.

4 cases of diastolic hypertension (3 women and 1 man) were found among the new immigrants, and 17 (7 men, 10 women) among the settled group. There was no statistical difference between men and women in each age-group of the " new " and " settled " groups in the prevalence of diastolic hypertension or involutionary sclerosis, except for ages 30–55. Except in this group, men and women were grouped together. (Fisher's exact method yields relatively low probabilities even for each sex and age group separately.). The prevalence of hypertension is shown in table II.

TABLE II—PREVALENCE (AS A PERCENTAGE) OF DIASTOLIC HYPERTENSION IN THE TWO GROUPS

—	30–55 years	Over 55 years
New	1% (0 M, 2 F)	7% (4 M, 11 F)
Settled	7·5% (7 M, 8 F)	20% (20 M, 21 F)
P	0·03	0·04

Proteinuria was found once in the 4 hypertensives among the new immigrants, and five times in the 17 hypertensives among settled Yemenites.

It is of interest that, though there were no diabetics among the new immigrants, there were 9 among the settled group (6 men and 3 women), 8 being more than 60 years old.

The percentage of cases with involutionary sclerosis, but without diastolic hypertension or diabetes, among the new immigrants and old settlers is given in table III.

TABLE III—PREVALENCE (AS A PERCENTAGE) OF RETINAL INVOLUTIONARY SCLEROSIS IN THE TWO GROUPS

—	30–55 years			Over 55 years		
	Total	M	F	Total	M	F
New	3%	0	5	8%	9	6
Settled ..	18%	7	27	34%	26	33
P		0·16	0·002		0·006	

There was a statistically significant difference in the prevalence of involutionary sclerosis between the " new " and " settled " in the age-group 55+ and between " settled " and " new " women in the age-group 30–55. No significant difference was found in the men of the age-group 30–55.

Discussion

It can be seen that there is a greater prevalence of diastolic hypertension, and of the ageing process as seen in the retina, among the Yemenites who have lived in Israel for over 25 years as compared with Yemenite new immigrants who have not lived for more than 10 years in the country. The findings parallel the differences in the prevalence of diabetes, and in the blood-cholesterol and blood-phospholipids estimates between both groups and confirm the impression that cardiovascular disease and arteriosclerosis are more prevalent in the settled group.

There is a great difference between the conditions of life in Israel and in Yemen, and there is little doubt that the different prevalences of hypertension and involutionary sclerosis between the two groups is the result of these differences. The lack of intermarriage with other groups of Jews eliminates constitutional and genetic factors as an explanation of the differences. The main differences between the two groups are in food habits and in the general strain of living to which they are exposed. The latter can be best described as the ambition for a higher standard of living, and the general " speeding-up " involved in the Western style of culture.

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RADIOLOGICAL LUNG-FUNCTION STUDIES

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WE describe here a method of measuring and recording the changes in radiographic lung density during respiration. We suggest that the function of a localised area of lung may be studied by correlating these density variations with simultaneous spirometric recordings.

Attempts have been made by Kjellberg et al. (1950) to study variations in pulmonary blood-flow by recording lung-density variations, using an electrokymographic method described by Engström et al (1949). Marchal et al. (1946, 1949, 1959) have studied lung-density variation during respiration, paying particular attention to the pulsation of the pulmonary arteries. These authors have also found that the variation in density of each lung during respiration correlates well with bronchospirometric findings. Other workers (Simonin et al. 1950, 1951) have attempted to study lung function by photometric comparison of the film densities on inspiration and expiration of similar areas of lung, radiographed through a kymographic grid. They have compared this method with electrokymographic measurements of lung density, and compared both methods with bronchospirometry.

Methods

Description of Apparatus

The apparatus is illustrated in figs. 1a and b.

The image of the lung field, formed on the phosphor of a 5-in. Philips image-intensifier, is viewed through a binocular eyepiece to establish the exact area under examination. A photomultiplier (R.C.A. type 913) in a special mounting is substituted for the eyepiece. An iris diaphragm is fitted to the

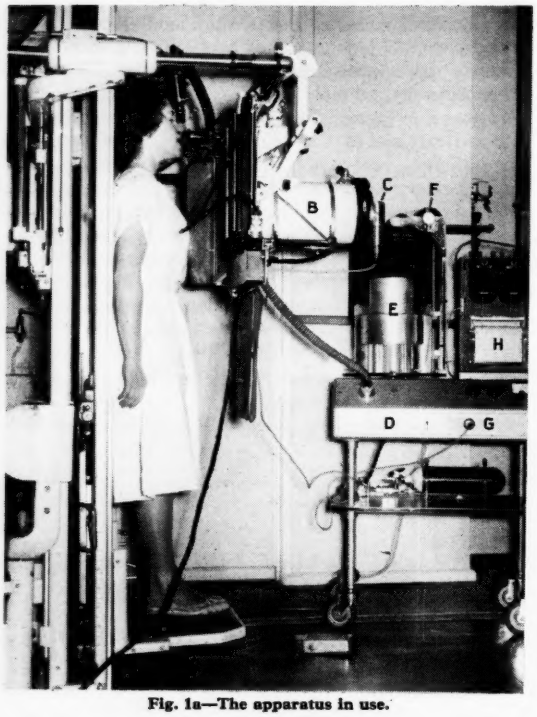

Fig. 1a—The apparatus in use.

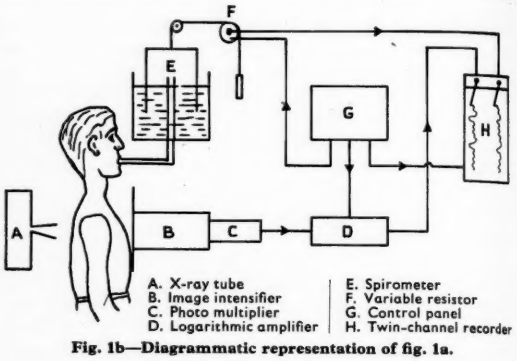

Fig. 1b—Diagrammatic representation of fig. 1a.

photomultiplier to protect it from daylight when it is not in use, and this is opened to a predetermined aperture when in use.

The electrical output from the photomultiplier is fed into a logarithmic amplifier (Sweet 1946), and, after further linear amplification, drives one pen of an Evershed two-channel recorder. In view of the known logarithmic absorption of X rays in soft tissues, a logarithmic amplifier was chosen in order to obtain a linear recording over the required density range (figs. 2a and b). The second pen is used to record the position of a spirometer bell. Movement of the bell moves a slider on a variable linear resistor, causing variations in an electrical current capable of operating the pen without amplification.

The Evershed recorder was selected for this application as it utilises a wide record-chart (2·9 in. per channel), is robust, and is easily operated. The record paper moves 6 in. per minute.

Sensitivity controls for both channels, the zero-setting control, and the on-off-switch for the record motor are grouped on a panel at the front of the instrument. A centre-zero meter indicates balance conditions, and allows the operator to make necessary adjustments to gain and sensitivity before a recording is started. The complete instrument is mains-operated and all power supplies are stabilised by an 'Advance' constant-voltage transformer (type CVH. 125).

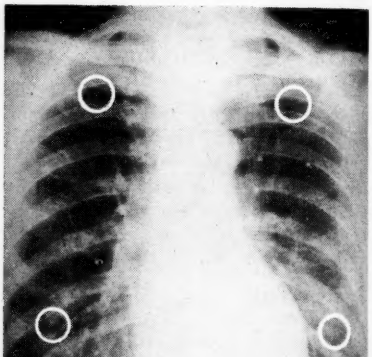

Fig. 3—The sites at which the lung-density recordings are usually made.

Method of Application

The patient is screened using a Philips image-intensifier. This examination can be carried out in daylight with a screening current of 0·5 mA at 40–50 kV. The density variations on the fluorescent screen of the amplifier are recorded by the photometer. The field examined is usually a circle of 5 cm. diameter, limited by a lead diaphragm between the patient and amplifier. The sites selected for examination are the areas immediately below the clavicles, and those above the diaphragmatic domes, symmetrically on the two sides (fig. 3). These sites are selected on preliminary screening with the binocular eyepiece, care being taken that, on full inspiration or expiration, neither the mediastinum nor the diaphragmatic domes enter the field. The eyepiece is then replaced by the photoelectric cell for the actual measurement. The anode-amplifier distance is kept constant, and no stationary grid is required.

The respirations of the patient are recorded by means of the spirometer while the radiographic density recording is being made.

After a rehearsal with the patient, recordings are made of breathing at an ordinary rate and amplitude, on deep respiration, and on forced

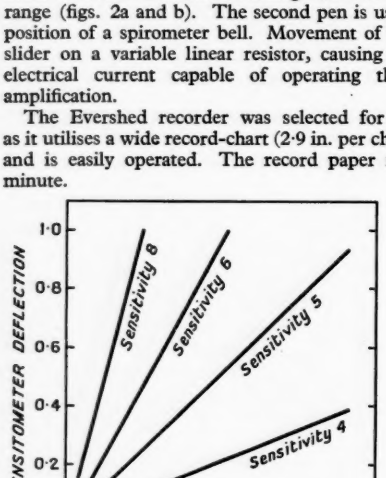

Fig. 2a.

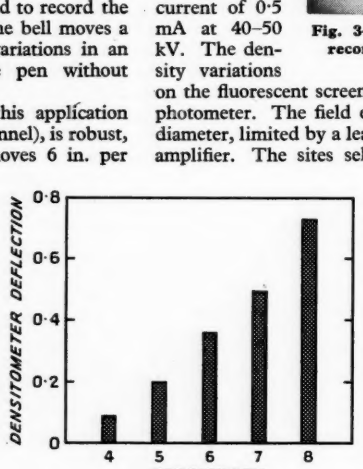

Fig. 2b.

Fig. 2a—Deflection obtained with an aluminium step wedge, using the densitometer at various sensitivity settings.

Fig. 2b—The average densitometer deflection obtained per mm. of aluminium at different sensitivity settings.

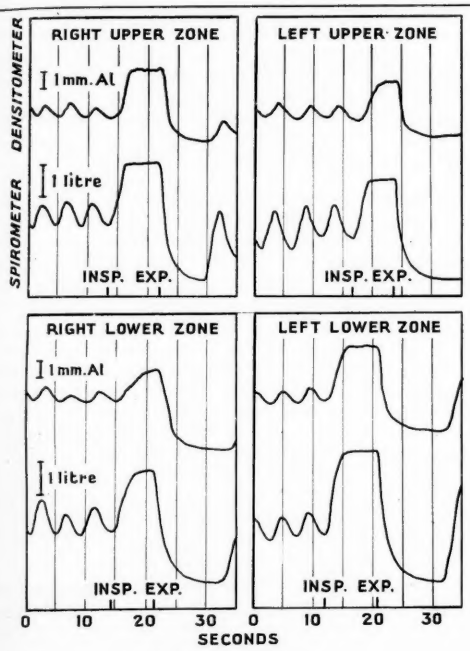

Fig. 4—Normal man.

In all recordings an upward deflection of the densitometer indicates brightening of the lung-field; an upward deflection of the spirometer indicates inspiration. The densitometer and spirometer tracings are synchronous.

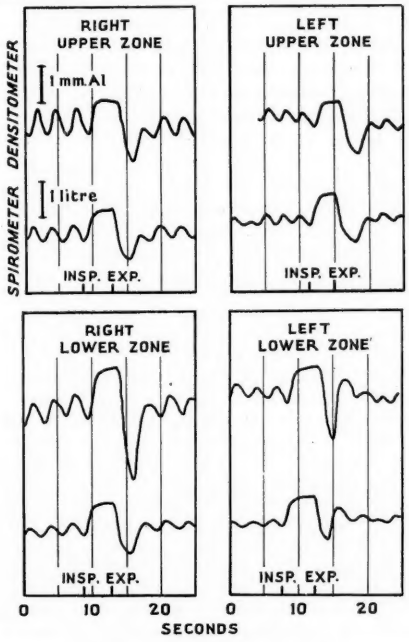

Fig. 5—Normal woman.

The records on the two sides are symmetrical, and the densitometer and spirometer recordings are synchronous.

expiration after a full inspiration. The aim is to obtain comparable respiratory excursions and similar spirometric tracings during the examination of each of the four selected areas.

The sensitivity of both the densitometer and the spirometer is varied from patient to patient, but, whenever possible, these factors are kept constant for individual patients so that curves obtained from different areas may be directly compared. It has been possible to calibrate the curves obtained with each sensitivity setting—the spirometer curve in litres of air and the densitometer in millimetres of aluminium—so that tracings made at different recording sensitivities may be indirectly compared. This calibration is purely for comparative purposes and no attempt is made to measure absolute values.

Results

Normal Recordings

The density curves obtained are usually symmetrical in comparable areas of each lung. There is a suggestion of less density variation in the upper than in the lower zones but this difference is not firmly established. There is good correlation, both in timing and amplitude, between the respiratory and density curves. The density curve is usually smooth but a ripple, synchronous with the heart beat, is sometimes superimposed. Since this effect can be accentuated by arresting respiration and by increasing the sensitivity of the densitometer, it probably represents the variation in pulmonary density due to the vascular component.

On forced expiration, following a full inspiration, the curves obtained from the densitometer and spirometer are almost synchronous and are similar in shape. The steepest part of both curves is during the early part of expiration, becoming shallower towards the end of expiration when both the densitometer curve and spirometer curve flatten out. If expiration is maintained both curves remain flat, but rise simultaneously on the next inspiration (figs. 4 and 5).

Abnormal Recordings

If there is unilateral lung disease, reference to the normal side simplifies the analysis of the curves. When the disease is bilateral, comparison has to be made with normal controls.

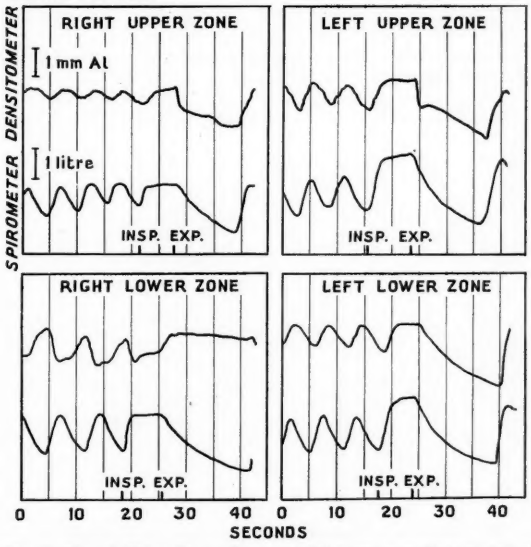

Fig. 6—Case 1. Recordings of a man with severe emphysema most marked in the right lower zone.

The most important feature is the asynchronous tracings in the right lower zone, thought to indicate abnormal air flow within the lung. A faint ripple seen on some of the densitometer tracings is attributed to the vascular component.

Analysis of the density curves is concerned with (1) the amplitude of the density variation in relation to the spirometer tracings, and (2) alterations in the time relationship between the two tracings.

To illustrate these points two examples are described.

Case 1. *Pulmonary emphysema with bullous emphysema of the right lower zone.*—The spirometer tracings were similar during the examination of each of the four areas. Normal respiration with a tidal flow of 1000–1200 ml. of air was followed by a full inspiration (held for approximately 5 sec.) and finally the forced expiration of approximately 2000 ml. of air. The forced expiration was considerably slower than in the normal subject (fig. 6).

In the areas examined, the density tracings show considerable differences in amplitude and timing. The left lower-zone tracing appears almost normal, following the spirometer curve closely. The curve is synchronous with the spirometer tracing and the only abnormality is that, on forced expiration, the rate of loss of density is less than in the normal. In the left upper-zone tracings, on forced expiration, there is a rapid initial loss of density, followed by a sudden check, and then a more gradual loss of density. This contrasts with the smooth curve obtained from the lower zone. The density tracing in the right upper zone is similar on forced expiration, but there is very little variation in lung density on normal respiration. The density tracing in the right lower zone is grossly abnormal. The density and spirometer curves are completely out of phase. During respiration, the lung becomes more dense on inspiration and less dense on expiration. On forced expiration, the lung initially becomes a little less dense and then shows no further change, even though the spirometer curve indicates that air is being expired from the lungs as a whole.

Comment.—The left lower zone is the area in which the tracings are nearest to normal. There is the good synchronous variation in density with respiration, and an even loss of density on forced expiration. This suggests that the most useful air movement is taking place in this area of the lung. The upper zones, by comparison, show little variation in density on respiration. On forced expiration, the sudden check in the density curve suggests that there is partial air-trapping after the start of expiration.

The curves in the right lower zone are paradoxical; the density curve shows brightening on expiration. The explanation for this is not known, but it may be due to air movement within the lungs, the air flowing into this region from other parts of the lungs.

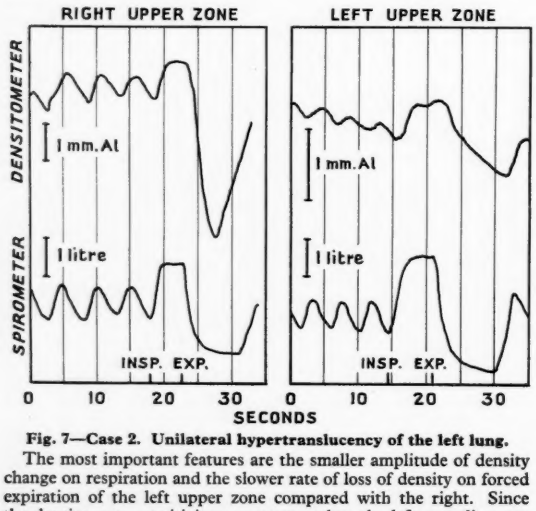

Fig. 7—Case 2. Unilateral hypertranslucency of the left lung.
The most important features are the smaller amplitude of density change on respiration and the slower rate of loss of density on forced expiration of the left upper zone compared with the right. Since the densitometer sensitivity was greater when the left recording was made, the difference between the two sides is greater than appears at first sight.

Case 2. *Radiological translucency of one lung.*—A young man, without symptoms, was found, on routine X-ray examination, to have unilateral hypertranslucency of the left lung (Macleod 1954). The right pulmonary arteries appeared normal but the left pulmonary arteries appeared abnormally small. Fluoroscopic examination showed that on expiration the left lung failed to deflate fully and the mediastinum swung to the right.

The tracings obtained for the right and left upper zones are shown in fig. 7. The spirometer tracings were similar when the two areas were examined. The density and spirometer curves show synchronous movement. But on normal respiration there is a much smaller amplitude of density change in the left upper zone when compared with the right. On forced expiration, there is a much slower rate of loss of density in the left than in the right lung. Similar changes were found in other zones. It should be noted that the densitometer sensitivity was greater when recording the left side than when recording the right side (see scale fig. 7), which means that the actual difference in density is greater than appears on the graphs.

Comment.—The small variation in lung density on normal respiration and the slow loss of density on forced expiration probably indicate that there is a much reduced air flow into and out of the left lung when compared with the right.

Discussion

A number of factors, pulmonary and extrapulmonary, influence the overall radiolucency of the lung-fields during respiration. The extrapulmonary factors are the ribs and soft tissues of the thoracic cage. Their influence on the density curves is small. On inspiration, the girth of the thoracic cage increases, thinning the overlying soft tissues and making them slightly more radiolucent. This change is in phase with and slightly augments the overall pulmonary density curve. The change in density caused by the ribs moving across the field during respiration is less regular than the soft-tissue effect. By choosing a 5 cm. diameter field, it is possible to even out the density changes produced by the ribs. For example, the effect of the ribs and soft tissues over a pneumothorax, when no lung is in the field, is small compared with the changes in density over a normal lung field.

The variation in radiolucency attributable to the pulmonary components are due to changes in blood contents and changes in air contents; the vascular component causes only a small ripple on the relatively large pulmonary density curve. The main density changes are due to the air component.

Sokolov (1956) has shown, by inflating the lungs of cadavers under experimental conditions, that the decrease in density which occurs with pulmonary inflation is dependent upon the total amount of lung tissue through which the X rays pass, and that this depends mainly on the amount of lung expansion which takes place in directions perpendicular to the rays. Thus, in an anterior view of a lung, the decrease in density is influenced mainly by expansion in the vertical and transverse directions, in the coronal plane, and only little by expansion in the anteroposterior direction.

The alterations of lung density during respiration, recorded by our densitometer, are a function of the degree of expansion of the part of lung under observation, and hence of the amount of air exchanged. Since the observations are carried out under dynamic conditions, the curves give some indication of the air flow into and out of this part of the lung. There is a recognisable normal pattern of tracings in different parts of the lung fields. When there are abnormalities, correlation of the density tracings in the different areas with the spirometer tracings

allows one to detect abnormalities of air flow. When alterations in lung density occur without spirometer movement, intrapulmonary air flow must be taking place. When there is localised air trapping, the densitometer tracing may show a slow rate of loss of density even though the spirometer tracings may be relatively normal. Normally the densitometer and spirometer tracings are synchronous. Asynchronous curves imply localised air-flow obstruction, or even reversal, as in one of our cases.

The place of this radiological technique in the study of lung function has not yet been fully assessed. It is hoped to correlate this method with other more conventional lung-function tests in order to establish its clinical value as a routine procedure.

Summary

A radiological method of studying localised changes in lung density during respiration is described. Simultaneous spirometer recordings are made.

The curves obtained in normal and abnormal patients are described and analysed.

The significance and interpretation of these findings is discussed.

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OPTIMAL PERFUSION-RATE IN HÆMODIALYSIS COMBINED WITH ULTRAFILTRATION

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IN acute renal insufficiency patients not infrequently become overhydrated as water is liberated from the cells by catabolic processes. Water is also formed by oxidation of body fat and dextrose. To prevent overhydration the intake of water must be rigorously restricted (to 400–500 ml. per day) during the anuric phase. Overhydration may lead to pulmonary œdema and bronchopulmonary infection; and cerebral œdema sometimes causes convulsions, especially when too much sodium has been given in an attempt to correct acidosis.

If progressive uræmia is complicated by severe overhydration, treatment with combined hæmodialysis and ultrafiltration is indicated. Ultrafiltration occurs if the pressure in the extracorporeally circulating blood (i.e., the colloid-osmotic pressure of the plasma) is at least 30 mm. Hg higher than the pressure in the surrounding bath fluid; this is technically feasible only if the filter membrane (' Cellophane ') is supported by a rigid screen which prevents changes of the extracorporeal blood-volume. Kolff's rotating kidney lacks this support, and therefore cannot be used as an ultrafiltrator. Kolff's twin-coil kidney, however, is supported; in this type of kidney ultrafiltration is obligatory because the high inner resistance of the narrow cellophane coils demands a high perfusion pressure. But the Skegg-Leonards and Alwall types of kidney seem preferable because they both give support to the cellophane membrane and allow controlled ultrafiltration.

Method

In our department a modified Alwall dialyser has been used since 1952. Under standard conditions the patient loses no water. As the inner resistance of the cellophane tubing spiral is low, a moderate perfusion pressure suffices for satisfactory flow. This slight " over " pressure is partially compensated by the colloid-osmotic pressure and partially by the hydrostatic pressure of the bath fluid. If the direction of flow through the cellophane spiral is from above downwards, the proximal coils will cause some ultrafiltration because the blood-pressure is high and the hydrostatic pressure of the bath fluid is low. The distal coils will take up water from the bath because the perfusion pressure is low and the hydrostatic pressure of the bath is high. In practice this maintains the water balance, as is shown by weighing the patient with a bed scale before, during, and after dialysis. The bath fluid we use is not hypertonic to uræmic plasma.

Ultrafiltration is made possible by placing an airtight lid on the bath-fluid reservoir, so creating a negative pressure in the air above the bath fluid. The hydrostatic pressure in the bath will thus be lowered, and a pressure gradient will be established between bath fluid and blood. This method has several disadvantages, including the high cost of airtight apparatus, the maintenance of a constant vacuum, and the sudden changes in blood-volume which arise during the rapid creation of a vacuum (although these changes are limited by the screen support, they may disturb the patient). A much simpler, cheaper, and easier way is to raise the pressure of the circulating blood. This can be done by using a higher perfusion-rate, and by increasing the resistance in the circuit by constricting the outflow tube from the " kidney " to the

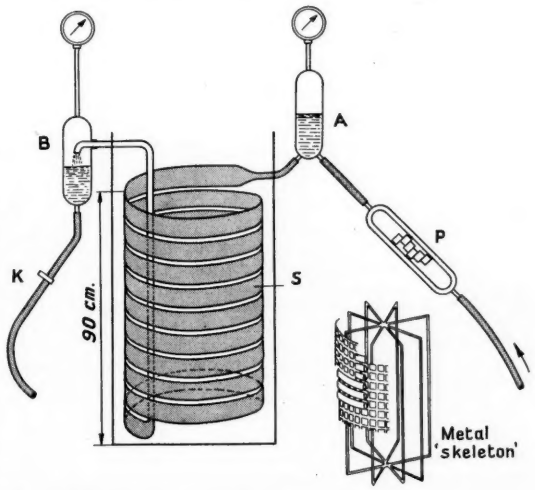

Fig. 1—Schematic drawing of the Alwall kidney as ultrafiltrator. P=finger pump. A and B=manometers respectively proximal and distal to the cellophane spiral, S. K=adjustable screw.

patient. Fig. 1 illustrates our technique, using a dialyser with 18 m. of cellophane tubing.

The perforated metal cylinders which form the screens for the cellophane spiral must be reinforced by a metal "skeleton". The inner cylinder would otherwise be damaged during operation by the considerable pressure resulting from application of positive pressure over a large surface. Blood is pumped from the patient by a 'Sigma' finger pump with adjustable speed (fig. 1, P). The pump can be adjusted to 'occlusive" setting, which makes the rate of blood-flow relatively independent of the pressure head in A. A is a simple manometer system which records the blood-pressure before it enters the proximal cellophane coils. S is the cellophane spiral where ultrafiltration takes place. This spiral is immersed in bath fluid. B is a manometer system which records the blood-pressure as it leaves the distal coils. The outflow tube can be narrowed by an adjustable screw, K, whereupon the pressure in B and in A will increase. By using manometers A and B various pressure-flow relations can be recorded; this system also allows the blood flow-rate to be measured in vitro.

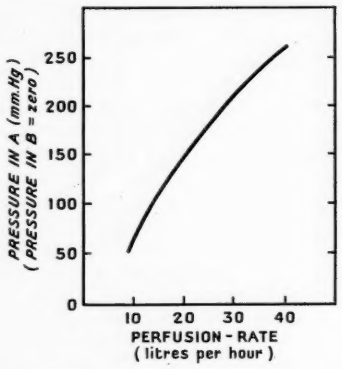

Fig. 2—Pressure-flow relations in ultrafiltration with an 18 m. cellophane tube, and without constriction of outflow tube.
The pressure in A reaches 200 mm. Hg at a perfusion-rate of 30 litres per hour.

Fig. 2 shows the increase in pressure in A when the rate of flow is increased without raising the pressure in B by creating a resistance at K. As maximum safe pressure we have empirically chosen 200 mm. Hg. Above this pressure the inner cylinder may be damaged (even when reinforced) or the cellophane tube may leak. 200 mm. Hg pressure in A is achieved with a flow-rate of 30 litres per hour.

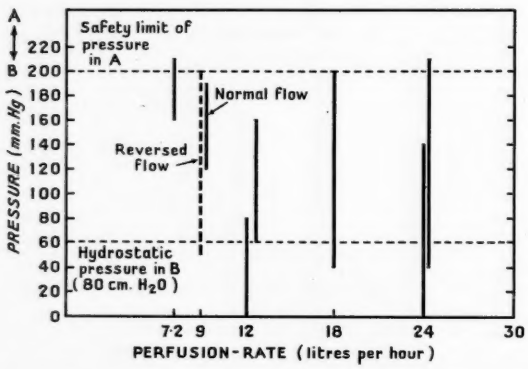

Fig. 3—Pressure-flow relations with an 18 m. cellophane ultrafiltrator.
Pressure at B is variably increased. Only moderate perfusion rates allow the pressure at B to increase considerably without excessive increase at A.

Fig. 3 shows the pressure-flow relations if the resistance at R is increased. Each vertical column represents at the top the pressure in A, and at the bottom the pressure in B, at a certain flow-rate. High flow-rates do not permit high pressures in B, because the pressure in A would then pass the safety limit. Ultrafiltration will be most efficient, however, if it takes place along the whole length of the cellophane tubing, and for this a high pressure is necessary in B. This can only be obtained with a moderate perfusion-rate. Too low a rate is unfavourable because the blood becomes excessively dehydrated, and ultrafiltration is handicapped by increasing colloid-osmotic pressure. A moderate flow of 10–12 litres per hour seems to be best for ultrafiltration. If the direction of blood-flow is reversed (from below upwards) the pressure difference between A and B increases considerably because the hydrostatic pressure of the bath fluid has now to be overcome at A. The resulting mean pressure $\frac{(A+B)}{2}$ is lower than with a normal flow; hence the direction of the blood-stream should be downwards.

The efficiency of dialysis is greater if the flow-rate is increased (fig. 4). High perfusion-rates (20–30 litres per hour) result in rapid clearances and consequently short dialyses. If dialysis is combined with ultrafiltration, however, moderate flows of 10–12 litres per hour seem preferable.

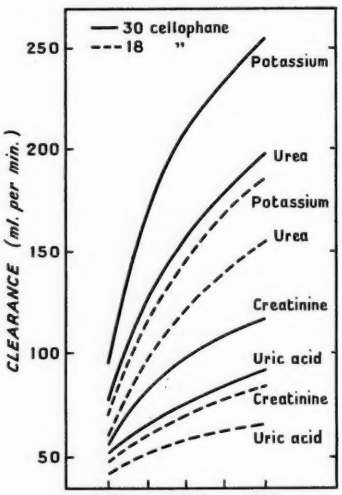

Fig. 4—In-vitro clearances of the Alwall kidney at different perfusion-rates.

We observed in vitro a water extraction of about 300 ml. per hour—a figure which correlates well with our clinical experience and with other published data. Higher rates of dehydration may lead to shock and hypotension. The above rate was well tolerated by overhydrated patients, and it did not cause hypotension, although hypertension was sometimes reduced to normal.

Summary

The artificial kidney of the Alwall type can be used for controlled ultrafiltration by creating a pressure difference between the extracorporeally circulating blood and the bath fluid.

The optimal flow-rate for ultrafiltration is lower than that for dialysis.

In clinical ultrafiltration water extraction of 300 ml. per hour did not lead to hypotension if the patient was overhydrated.

STAPHYLOCOCCAL PNEUMONIA IN THE NEONATAL PERIOD

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THE pattern of tissue reaction to microbial infection varies with the virulence of the organism, the resistance of the host, and occasionally with the portal by which the organism gains access. Neonatal lung infection with the staphylococcus illustrates this point.

We describe here eight examples of staphylococcal pneumonia in the neonate which occurred during the period March, 1958, to August, 1959. They illustrate the often fulminant character of the infection and the variety of histological appearances in the lungs, and emphasise the need for the diligent use of the aseptic method in the care of the newly born.

Illustrative Case-record

Stillborn infant, aged 39 weeks. The mother, a multipara aged 31, was admitted with toxæmia on Aug. 5, 1959, at 37th week of pregnancy. She was kept in bed, but her hypertension did not lessen and it was decided to induce labour by hind-water rupture of the membranes; this was done on Aug. 14. The next day an oxytocin (' Pitocin ') drip was given which induced uterine contractions.

The temperature rose to 105°F on the following day, with a rigor; tenderness was noted in the right loin and right iliac fossa. A diagnosis of pyelitis of pregnancy was made; urine examination showed a few pus cells, and *Proteus vulgaris* was cultured. A high vaginal swab produced a growth of *Staphylococcus pyogenes*, sensitive to most antibiotics; the organism was not present in the patient's nose. Benzyl penicillin (penicillin G) 500,000 units and streptomycin 0·5 g. were given twice daily. On the same day, when the cervix was two finger breadths dilated, at approximately 1.30 P.M., the fœtal heart sounds became inaudible.

She was delivered at 3.45 P.M. on Aug. 16 of a stillborn male fœtus weighing 5¼ lb. (2410 g.). Her temperature became normal next day, and recovery was uneventful.

Necropsy

Tiny hæmorrhages were scattered over the visceral pleuræ of both lungs and over the visceral pericardium. Small quantities of blood-stained fluid were seen in both pleural and pericardial cavities. The spleen weighed 14 g., and appeared normal.

No other abnormality was found. The placenta and umbilical cord appeared normal macroscopically.

Histological Findings

Lungs.—All lobes of the lungs contained areas of intra-alveolar hæmorrhage, mingled with clusters of polymorphonuclear leucocytes and clumps of staphylococci. There were numerous epithelial squames in alveoli and alveolar ducts. A few veins contained thrombi.

Placenta.—Areas of purulent infiltration were seen in sections of placenta and umbilical cord.

Bacteriological Investigations

The lungs and spleen were examined by the method described by Gresham and Gleeson-White (1957). All lobes grew a strain of *Staph. pyogenes*, sensitive to all antibiotics against which it was tested (case 8, table III). The spleen was sterile.

The findings in the other cases in this series are summarised in table I.

Discussion

All infants showed histological evidence of pneumonia which varied from predominantly hæmorrhagic to frankly purulent infiltration. In every case *Staph. pyogenes* was isolated from the lungs.

The histological appearances in the lungs could be classified broadly into three main groups:

1. Extensive intra-alveolar hæmorrhage with necrosis of alveolar walls, together with abundant staphylococci. Polymorphonuclear leucocytic infiltration was scanty. This appears to represent an overwhelming infection—the organism being at the peak of its virulence and the host resistance low. Two cases (1 and 6) fall into this group.

2. Five showed the usual appearances of bacterial bronchopneumonia with sparse intrapulmonary hæmorrhage. The duration of illness in these cases (3–7) was of the order of days rather than hours, as in the first group.

3. One showed sparse polymorphonuclear leucocytic infiltration in alveoli (case 2). The staphylococcus was isolated both from the lung and from the spleen. The changes in the lungs reflected those seen in other organs and were due to septicæmia.

Five cases were infected with *Staph. pyogenes* of the same antibiotic resistance patterns as those of the indigenous hospital staphylococcus. This suggested that the source of infection was the hospital environment. The route of infection in at least four of these was probably vaginal; three showed placentitis on histological examination. In one (case 7) the infant was delivered at another hospital and the placenta was not available. Nevertheless, the mother's vagina contained a *Staph. pyogenes* similar in antibiotic resistance pattern to that isolated from the fœtal lung. The finding of placentitis strongly supports the view that the bronchopneumonia in the fœtus was due to inhalation of infected amniotic fluid. Further evidence

TABLE I—CLINICAL FEATURES

Case no.	Antenatal history	Duration of pregnancy in weeks	Delivery	Stillbirth or neonatal death	History of infant	Duration of life
1	Essential hypertension; toxæmia. P.R.M.	31	Normal	N.N.D.	Neonatal asphyxia; intragastric oxygen	42 hours
2	5 threatened abortions. P.R.M.	30	Normal; fœtal distress	N.N.D.	Neonatal asphyxia; intragastric oxygen	37 hours
3	2 false labours	42	Normal; fœtal distress	N.N.D.	Neonatal asphyxia; intragastric oxygen	4 days
4	Emergency admission at full dilatation	36	Normal	N.N.D.	Not intubated	11 days
5	Toxæmia. P.R.M.	38	Normal	N.N.D.	Not intubated	18 days
6	Eclampsia. P.R.M.	33	Cæsarean section	N.N.D.	Not intubated; oxygen by positive-pressure mask	36 hours
8	Toxæmia. A.R.M.	39	Oxytocin drip: rigors during labour; temp. 105°F; fœtal distress; N.D.	S.B.	Not available	Not known

P.R.M. = premature rupture of membranes; A.R.M. = artificial rupture of membranes; S.B. = stillbirth; N.N.D. = neonatal death; N.D. = normal delivery.

TABLE II—PATHOLOGY

Case no.	Weight (g.)	Ossification centres	Lung	Œsophagus	Other organs	Placenta
1	1320	C	Lung hæmorrhage; pneumonia; squames ±	Œsophagitis	Normal	No inflammatory changes
2	955	C, Ta	Pneumonia; squames ++	Œsophagitis	Normal	Inflammatory reaction in placenta and cord
3	1397	C, Ta	Bronchopneumonia; squames ++	Œsophagitis	Normal	Inflammatory reaction in placenta and cord
4	2270	C, Ta, F	Bronchopneumonia; no squames	Normal	Meningitis; hydrocephalus; meningomyelocele; spina bifida; C.D.H.	No infection
5	1620	C, Ta, F, Ti	Bronchopneumonia; no squames	Normal	Meningitis; pericarditis; microcephaly; proptosis; spina bifida	Not available
6	1122	C, Ta	Lung hæmorrhage; bronchopneumonia; squames ±	Normal	Normal	No infection
7	1055	C, Ta	Bronchopneumonia; squames ++	Normal	Staphylococcal enteritis	Not available
8	2410	C, Ta, F	Bronchopneumonia; squames ++	Normal	Normal	Inflammatory reaction in placenta and cord placentitis

Ossification centres: C=calcaneum, Ta=talus, F=lower end of femur, Ti= upper end of femur, cuboid.
C.D.H. =congenital dislocation of the hip. ++=many, ±=few

TABLE III—BACTERIOLOGY

Case no.	Interval from death to bacteriological examination	Bacteriological examination of infant							Bacteriological examination of mother							Interval from delivery to bacteriological examination
		Lung	Spleen	Sensitivity					Nose and Throat	Vagina	Sensitivity					
				Penicillin	Tetracycline	Erythromycin	Streptomycin	Chloramphenicol			Penicillin	Tetracycline	Erythromycin	Streptomycin	Chloramphenicol	
1	4 days	*Staph. pyogenes*	Negative	R	S	S	S	S	Negative	Negative	..	..	..	..	..	5 days
2	3 days	*Staph. pyogenes*	Positive	S	S	S	S	S	Negative	*Staph. pyogenes*	S	S	S	S	S	2 days
3	2 days	*Staph. pyogenes*	Negative	R	S	S	S	S	Negative	Negative	..	..	..	..	..	73 days
4	4 days	*Staph. pyogenes*	Negative	R	S	S	S	S								Not made
5	2 days	*Staph. pyogenes*	Negative	R	S	S	S	S								Not made
6	3 days	*Staph. pyogenes*	Negative	S	S	S	S	S	Negative	Negative	..	..	..	..	..	5 days
7	6 days	*Staph. pyogenes*	Negative	R	S	S/R	R	S	Negative	*Staph. pyogenes*	R	S	S/R	R	S	2 days
8	2 days	*Staph. pyogenes*	Negative	S	S	S	S	S	Negative	*Staph. pyogenes*	S	S	S	S	S	Same day

S=sensitive. R=resistant.

for the view that inhalation was the route of pneumonic infection is provided by the occurrence of fœtal distress, and the presence of numerous amniotic squames in the air-passages of all infants in which this route is postulated. A vaginal route of infection is also supported by the fact that an undue number of vaginal procedures were made in the antenatal period; these were carried out because of a high incidence of antenatal complications in these mothers (table I).

The sensitivity of the organisms to various antibiotics is shown in table III. Three strains were sensitive to all the antibiotics against which they were tested. These three organisms were probably derived from the mothers themselves, or from a newly introduced strain carried into the ward. Case 8 (table I) is typical; a high vaginal swab from the mother before delivery showed a sensitive strain of *Staph. pyogenes*.

In three cases the mother's vagina did not grow *Staph. pyogenes* though it was isolated from the fœtal lungs. However, the interval of several days between delivery and taking a vaginal swab may explain this discrepancy.

Cases 4 and 5 (table I) were infants with congenital abnormalities. They survived much longer than all other infants in this series. The organism responsible for their pneumonia had the same resistance pattern as the indigenous hospital staphylococcus. They were probably infected post partum. There were no inflammatory changes of the umbilical cord or placenta in case 4. The other placenta was not available.

Three cases showed œsophagitis, associated with intubation and the administration of gastric oxygen. The lesion was probably incidental, and was not the primary source of infection.

All infants were premature as judged by weight. The number of ossification centres found at necropsy varied from case to case (table III). Most were found in case 5—an infant with multiple congenital abnormalities. This suggests that such babies may be expected to develop lung infections, either because prematurity reflects antenatal complications and the need for excessive manipulations, or because they are unduly susceptible to infection.

Summary

Eight cases of fatal staphylococcal pneumonia in neonates are described. The infection was often fulminant, and a variety of histological appearances—ranging from extensive intra-alveolar hæmorrhage with necrosis of the alveolar walls to a slight polymorphonuclear leucocytic infiltration—were found post mortem.

The causal organism in every case was *Staphylococcus pyogenes*. It is suggested that in six of the infants the bronchopneumonia was due to the inhalation of infected amniotic fluid; two cases were probably infected post partum. The need for diligent application of aseptic methods in the care of the newly born is stressed.

Our thanks are due to Dr. A. M. Barrett, Dr. D. M. T. Gairdner, and Dr. M. H. Gleeson-White for their cooperation in the preparation of this paper.

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GONADAL DYSGENESIS (TURNER'S SYNDROME) WITH MALE PHENOTYPE AND XO CHROMOSOMAL CONSTITUTION

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A BOY, aged 8, the eldest son of young parents, was admitted to the metabolic department on April 5, 1957, because of poor somatic development.

Maternal pregnancy and labour had been normal. General condition was fair. Height 3 ft. 9 in. (113 cm.); weight 45·4 lb. (20·6 kg.); span 3 ft. 7 in. (110 cm.) (fig. 1). Clinical examination revealed malformed external genitalia and some lesser congenital defects—low hair-line and ears, high-arched palate, and a number of nævi. The penis 1·2 in. (3·1 cm.) long, without urethral meatus, was bent ventrally by a web connecting the ventral surface to the perineum. Thus the "scrotum" appeared to be bifid, a depression with two small meatuses being visible in the midline; one communicated with the bladder through a short urethra, and the other led to a closed cavity (fig. 2). When the patient underwent plastic surgery, it was verified this cavity communicated with the uterus. No testes could be felt in the labioscrotal folds or in the inguinal regions. A rudimentary uterus was seen on peritoneoscopy and a laparotomy was done for further investigation of the internal genitalia. Near the small left tube was an elongated, almond-shaped mass $^{3}/_{8}$ in. (1 cm.) long, which was histologically a rudimentary testis (figs. 3 and 4). On the right, instead of an ovary, there was connective tissue, as seen in other cases of gonadal dysgenesis with negative chromatin pattern (Epps et al. 1958). 17-ketosteroids (Drekter) 0·8 mg. per 24 hours. Bone age of 7 years; X-ray examination of the skull, no abnormality. Colour-vision normal (Ishihara tests).

The nuclear sex in material obtained from the blood, oral smears, and from the skin biopsy was male. In the blood-smears, no "drumsticks" were found in 500 leucocytes counted. Chromosomal counts (Bottura and Ferrari 1960) in the 20 bone-marrow specimens examined gave a constant number of 45 chromosomes. In the 13 cells in optimal condition, 4 small acrocentric chromosomes could be positively identified. After pairing (fig. 5), the absence of a second medium-sized chromosome with subcentral centromere (probably an X chromosome) was noted. In view of these facts, the chromosomal constitution of the patient must be XO. The constancy of the number 45 in the chromosomal counts argues against

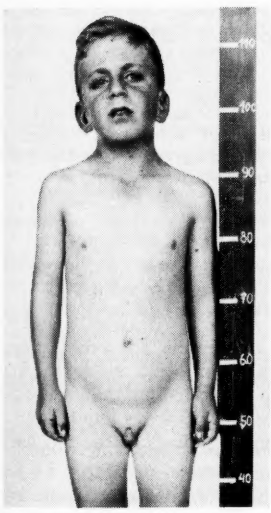

Fig. 1.

Fig. 2.

Fig. 1—Gonadal dysgenesis (Turner's syndrome) in a boy aged 8.
Fig. 2—The external genitalia.
Fig. 3—Embryonic testis.

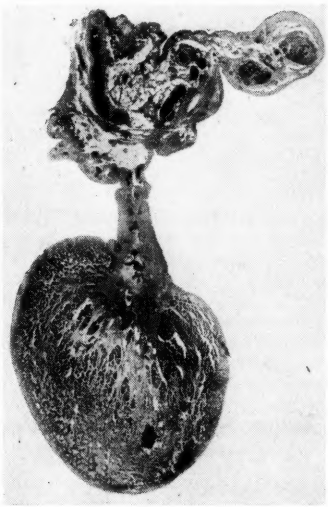

Fig. 3.

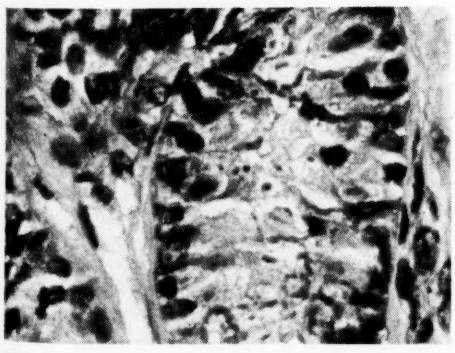

Fig. 4—Testicular tissue showing Sertoli cells, some undifferentiated germ cells, and spermatogonia. No later phases can be identified. Scanty and isolated interstitial cells are present. (Hæmatoxylin and eosin. × 220.)

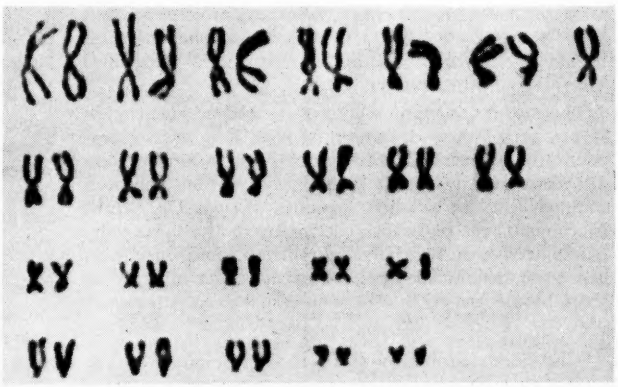

Fig. 5—Paired chromosomes from bone-marrow specimen, showing absence of one X chromosome.

the possibility of mosaicism as far as bone-marrow cells are concerned.

Discussion

XO chromosomal constitution in gonadal dysgenesis with female phenotype was described by Ford et al. (1959). A reasonable assumption from the study of our case is that XO chromosomal constitution is not incompatible with a male phenotype and with the presence of embryonic testis. Further instances of testicular development with a male phenotype without Y chromosome are represented by the XX true hermaphrodites recently reported (Harnden and Armstrong 1959, Hungerford et al. 1959, de Assis et al. 1960, Ferguson-Smith et al. 1960).

Summary

We describe a case of gonadal dysgenesis (Turner's syndrome) in a boy of 8. He had a rudimentary uterus, and an embryonic testis. No ovaries were found. The nuclear sex was male. " Drumsticks " were absent from the leucocytes. Only 45 chromosomes were present in the cells of all (20) bone-marrow specimens examined, and chromosome analysis pointed to the absence of one X chromosome. His phenotype is, therefore, male with an XO chromosomal constitution.

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PREMEDICATION WITH ATROPINE BY MOUTH

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IN 1872 Heidenhain demonstrated that the salivary secretion produced by stimulation of the chorda tympani was prevented by atropine, and, in the next year, Ebstein used it therapeutically in a patient with apoplexy. In 1875 Munro reported its use in cats for preventing early cardiac arrest during chloroform anæsthesia, but it was not until after 1890 that the subcutaneous injection of atropine before induction of anæsthesia came into general use in this country.

There seems to be no record of the oral administration of atropine before operation, though it is used therapeutically for various conditions. Even when sedative drugs are given by mouth preoperatively, it has still been common practice to inject atropine, though Dr. W. S. McConnell tells us he has used it by mouth effectively. In children it is especially desirable to avoid injections; hence we conducted this trial of the effect of atropine given by mouth.

The Trial

All children admitted to the Evelina Hospital, under the same surgeon and anæsthetist for tonsillectomy, were included in the trial. When admitted, the day before the operation, the child was placed in an " oral " or " subcutaneous " group by random allocation, the anæsthetist being unaware of the grouping. The trial lasted fifteen months, and ended when the anæsthetist ceased to work at this hospital.

240 children were admitted to the trial, but 93 were excluded because a different anæsthetist was working on that occasion or because the data were incomplete. There remained 147 children for study. Their sex, average weights, and ages were:

	No.	*Males*	*Females*	*Age (yr.)*	*Weight (lb.)*
Oral	74	41	33	6·5	49
Subcutaneous	73	39	34	6·7	51

and the age-distribution was:

	No.	*3–5 yr.*	*6–8 yr.*	*9–12 yr.*
Oral	74	21	44	9
Subcutaneous	73	17	45	11

The average interval between administration of atropine and induction of anæsthesia was 95 and 87 minutes for the oral and subcutaneous groups respectively.

During the night before operation the sleeping pulse was measured twice. Next morning, an hour before the expected time of operation, atropine was given—either 0·85 mg. by mouth or 0·64 mg. subcutaneously—with butobarbitone, in a dose of 75 mg. per stone body-weight. The pulse-rate was recorded again just before the child was taken to the operating-theatre, and the state of consciousness was noted. In the anæsthetic-room the size of the pupils was measured to the nearest millimetre by comparison with a prepared scale, and the reaction to light was noted. All patients were anæsthetised with ether after induction with either ethyl chloride on a Schimmelbusch mask or nitrous oxide and oxygen through a semiopen circuit. The degree of salivation was assessed during induction by inserting a finger into the buccal sulcus; if it was dry or slightly moist, it was recorded as O, if wet but not dripping off the finger as +, and if copious and stringy as ++. Additionally, if salivation interfered with induction, it was recorded as ++.

Results

Salivation

The degree of salivation was:

	No.	*O*	+	++
Oral	74	63	9	2
Subcutaneous	73	68	4	1

Excessive salivation was uncommon in either group, occurring only twice in the oral group and once in the subcutaneous group. There was a little more mild salivation in the oral group than in the subcutaneous group, but the difference was small and not significant at the 5% level.

Pupils

The average size of the pupils was identical in the two groups, and the incidence of negative reaction to light was similar:

	No.	*Size (mm.)*	*Negative reaction*
Oral	74	6·1	15 (*19%*)
Subcutaneous	73	6·1	11 (*15%*)

Pulse-rate

The response of the pulse-rate was:

	No.	*Before atropine*	*After atropine*	*Rise*
Oral	74	85	107	22
Subcutaneous	73	86	111	25

The mean rate before atropine was similar in both groups, there being a rise of 22 and 25 beats per minute in the oral and subcutaneous groups respectively.

Discussion

Dose

Unna et al. (1950) have shown that the smallest effective dose of atropine for suppression of salivation in children aged 3–12 years is about 0·007 mg. per kg. body-weight subcutaneously, or three times this dose by mouth. The dose for a 20 kg. child is about a quarter the dose of

0·64 mg. commonly used subcutaneously. Mushin and Galloon (1953) also regard 0·64 mg. subcutaneously as more than is needed to suppress salivation. Thus our subcutaneous dose was probably three times larger than necessary, and our oral dose was the smallest effective dose recommended by Unna et al.

Salivation

Although we evaluated the effect of atropine by several criteria, the suppression of salivation is especially important in premedication, and is also the most sensitive index of the effect of atropine (Unna et al. 1950). Our finding of excessive salivation in 2% was similar to the 4% observed by Marx and Orkin (1959), but their figures were for atropine and scopolamine, and they pointed out that their atropine group had more secretion than their scopolamine group.

During our study atropine was deliberately not given to a few patients, in order to establish that it had some effect. But the excessive salivation and extreme bradycardia in the first five children so treated made us unwilling to continue, and we resumed the trial. Mushin and Galloon (1953) pointed out that the degree of salivary depression necessary depended on the type of anæsthesia used, ether needing about 40% and nitrous oxide about 10% depression. We used ether, and therefore our patients needed maximum depression of salivation.

Pupils and Pulse-rate

Both mydriasis and tachycardia are unreliable signs of the effect of atropine, because anxiety, excitement, or barbiturates may also produce these signs; but atropine was probably responsible for mydriasis in some of our patients, as the correlation between size of pupil and reaction to light was significant:

	No.	*Size of pupil (mm.) with positive reaction*	*No.*	*Size of pupil (mm.) with negative reaction*
Oral	59	5·7±0·19	15	7·8±0·82
Subcutaneous ..	62	5·8±0·19	11	8·1±0·96

Difference in size of pupils is significant ($P = <0·05 > 0·02$).

We cannot be sure that the rise of pulse-rate was solely due to atropine, although it probably made a substantial contribution. The rise in pulse-rate was similar in both our groups.

We were unable to show any correlation between pupil size, rise in pulse-rate, and salivation. However, we found correlation between the size of pupil and its response to light, the fixed pupils having a mean diameter of 7·8 and 8·1 mm. (oral and subcutaneous) compared with 5·7 and 5·8 mm. for the active pupils. It is interesting that we found this correlation in the oral group, for Unna et al. (1950) pointed out that the smallest dose by mouth which suppressed salivation did not cause mydriasis or tachycardia.

The average time between giving atropine and inducing anæsthesia was 95 and 87 minutes in the two groups. This interval is similar to that observed by Unna et al. (1950), who found the greatest effect of atropine was between sixty and a hundred and twenty minutes for an oral group, and to that of Mushin and Galloon (1953), who found the greatest effect between sixty and ninety minutes for a subcutaneous group.

Our investigation has shown that, in children, atropine given by mouth is as effective as atropine given by subcutaneous injection. As it is desirable to avoid injection in children, the oral route seems preferable.

Summary

147 children randomly selected were given oral or subcutaneous atropine before anæsthesia, and the effects on salivation, pupils, pulse-rate, and anæsthesia were observed. No differences between the groups were found.

Thus is it concluded that atropine by mouth is satisfactory for premedication.

We wish to thank the nursing staff and residents at the Evelina Children's Hospital for their help, and Mr. L. F. W. Salmon for allowing us to conduct this trial on patients under his care.

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Preliminary Communications

ANTINUCLEAR FACTORS IN THE SERUM OF RELATIVES OF PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

DURING an investigation of antinuclear factors in the serum of patients with systemic lupus erythematosus (S.L.E.) we found a relationship between the titre of antinuclear factors in the serum and the clinical activity of the disease. High titres were found in patients with active S.L.E.; the titres were considerably lower in most patients in whom the disease was adequately controlled by treatment with prednisone.[1] As this test for antinuclear factors was sensitive, and as the results could be quantitated, we were prompted to examine the serum of relatives of patients with S.L.E. for antinuclear factors, particularly in view of recent reports of the familial occurrence of S.L.E.[2–8]

MATERIAL AND METHODS

Smears of fresh unfixed healthy human buccal mucosal epithelial cells were used as the source of the cell nuclei. After washing with 0·01 *M* saline phosphate buffer (pH 7·0) the slides were air-dried, and the smears were covered with a drop of the test serum. The smears were incubated for 90 minutes at room temperature in a moist atmosphere. The slides were washed for 30 minutes in three changes of buffer, air-dried, and layered for 30 minutes with rabbit antihuman γ-globulin conjugated with fluorescein isothiocyanate (Sylvana). They were washed and were then mounted in buffered glycerin. They were inspected for specific nuclear fluorescence, using a Reichert Zetopan microscope with an aplanatic dark field condensor (light source: Osram HBO 200 mercury-vapour lamp; Corning 5840 and Wratten 2A filters).

All tests were done in duplicate. When specific nuclear fluorescence was found, serial dilutions of serum (to 1 : 4096) were incubated with smears of buccal mucosal cells in a similar fashion. The highest dilution in which specific nuclear fluorescence was detected was called the " titre " of antinuclear factors.

Full details of the technique and controls used will be published elsewhere.[1] It was shown that duplicate titrations on the same sera gave identical titres in 4 of 10 instances. The final titres differed by only one dilution in the other 6.

RESULTS

The results are shown in table I. Single serum samples from 40 healthy subjects and 50 sera from 45 patients with

1. Mandema, E., Pollak, V. E., Kark, R. M. Unpublished.
2. Leonhardt, T. *Lancet*, 1957, ii, 1200.
3. Agranat, A. L., Bersohn, I., Lewis, S. M. *S. Afr. med. J.* 1957, **31**, 258.
4. Larsson, O., Leonhardt, T. *Acta med. Scand.* 1959, **165**, 371.
5. Lawrence, J. R. Personal communication, 1960.
6. Wagenhals, C. O., Burgeson, P. A. *N.Y. St. J. Med.* 1958, **58**, 98.
7. Griffin, S. W., Ulloa, A., Holley, H. L. *Arthrit. Rheum.* 1958, **1**, 544.
8. Holman, H. R., Deicher, H. *ibid.* 1960, **3**, 224.

TABLE I—TITRES OF ANTINUCLEAR FACTORS IN HEALTHY SUBJECTS, IN PATIENTS WITH VARIOUS DISEASES UNRELATED TO S.L.E., AND IN PATIENTS WITH S.L.E. AND THEIR RELATIVES

Titre of Antinuclear factors (dilution)	Healthy subjects	Diseases unrelated to S.L.E.	Patients with S.L.E.	Relatives of patients with S.L.E.
Negative:				
Undiluted ..	33	40	3	20
1 : 1	3	5	2	3
1 : 2	4	4	1	3
Positive:				
1 : 4 to 1 : 16	0	1	12	17
1 : 32 to 1 : 128	0	0	14	4
1 : 256 to 1 : 4096	0	0	19	3

diseases unrelated to S.L.E. were studied as controls. Specific nuclear fluorescence was not seen with 73 of these sera, and was seen with undiluted serum or serum diluted 1 : 2 in another 16 sera. In only 1 instance was specific nuclear fluorescence seen when the serum was diluted 1 : 4.

51 patients with S.L.E. were studied. When the first serum drawn from each of these patients was examined, specific nuclear fluorescence was found with serum diluted 1 : 4 or higher in 45. In all, 151 specimens of serum from these 51 patients have been examined to date, and specific nuclear fluorescence with serum diluted 1 : 4 or higher was observed with 131 specimens. As antinuclear factors were found when the serum was diluted 1 : 4 in only 1 of 90 sera examined as controls, the demonstration of antinuclear factors in serum diluted 1 : 4 or more appeared to distinguish patients with S.L.E. from healthy subjects and those with a variety of other diseases. The test was therefore called positive when antinuclear factors were demonstrated in serum diluted 1 : 4 or more.

TABLE II—RESULTS OF TESTS FOR ANTINUCLEAR FACTORS IN THE RELATIVES OF PATIENTS WITH SYSTEMIC LUPUS ERYTHMATOSUS

Relationship	Female relatives		Male relatives	
	Positive tests	Negative tests	Positive tests	Negative tests
Parents	5	1	0	4
Siblings	6	4	4	5
Offspring	2	0	2	3
Maternal siblings ..	3	1	1	1
First cousins	1	0	0	1
Grandparents	0	3	0	3
Totals	17	9	7	17

Single serum samples from 50 members of families of 12 patients with S.L.E. were studied (tables I and II). Specific nuclear fluorescence was demonstrated with serum diluted 1 : 4 or more in 24 instances. Positive tests were found with the sera of 19 of 36 first-degree relatives tested, and with the sera of 5 of 14 second-degree relatives. Positive tests were found in 17 of 26 female relatives but in only 7 of 24 male relatives. The difference in the frequency of positive tests in male and female relatives is significant ($\chi^2=5{\cdot}2$, $P=<0{\cdot}05$), but further observations on this sex difference are necessary.

Two family pedigrees are shown in fig. 1.

In the first pedigree the propositus (II.4) was a 15-year-old schoolgirl in whom definite clinical evidence of S.L.E. had been found, and, in the past, Hargraves' cells had been demonstrated in her blood. Findings diagnostic of lupus nephritis were observed in a renal biopsy. 4 specimens of serum were tested for antinuclear factors when the patient was symptom-free as a result of treatment with prednisone; all were negative. Positive tests for antinuclear factors were found in the mother (I.1) and 3 of 5 siblings—in 1 of whom (II.1) the titre was 1 : 1024.

In the second pedigree the propositus (II.2) was a 21-year-old American Negro housewife with typical S.L.E. Positive tests for antinuclear factors were found in the serum of the patient, her 2 younger sisters, her 5-year-old son, and 3-year-old daughter (III.3)—in whom the titre of antinuclear factors was 1: 4096.

The serum-γ-globulin levels were estimated by the Biuret reagent and filterpaper electrophoresis. They are compared in fig. 2 with values from 62 healthy Caucasian ($1{\cdot}13\pm0{\cdot}23$ g. per 100 ml.) and 62 healthy American Negro subjects ($1{\cdot}37\pm0{\cdot}30$ g. per 100 ml.). Elevated γ-globulin levels (> 2 S.D. above the mean of the controls) were found in only 3 Caucasian relatives and 2 Caucasian controls. Decreased γ-globulin levels (> 2 S.D. below the mean of the controls) were found in 1 Caucasian and 2 Negro relatives. 5 of the 6 Negro relatives were members of one family (pedigree 2). The difference between the γ-globulin levels in the members of this family and those in the controls was significant ($\chi^2=17{\cdot}2$, $P=<0{\cdot}01$).

DISCUSSION

In 1957 Leonhardt [2] reported S.L.E. in 3 of 14 siblings. He pointed out that at that time there were only four reported instances of the familial occurrence of S.L.E.

Subsequently, Agranat et al.[3] Larsson and Leonhardt,[4] and Lawrence [5] have each reported S.L.E. in 2 sisters. Wagenhals and Burgeson [6] observed the disease in twin sisters. Griffin et al.[7] found S.L.E. in a father and his daughter, and Holman and Deicher [8] reported its occurrence in a mother and her daughter. These clinical observations suggested that S.L.E. may possibly be a familial disorder.

In a study of two pedigrees, Larsson and Leonhardt [4] found higher mean serum-γ-globulin levels in siblings of patients with S.L.E. and their children than in controls living under the same environmental conditions. The siblings had higher mean γ-globulin values than the first cousins, and the siblings' children than the second cousins. Larsson and Leonhardt considered that familial hypergammaglobulinæmia and familial S.L.E. were possibly closely related and were manifestations of an underlying, genetically determined tendency to overproduction of γ-globulin. Holman and Deicher [8] found "distinct hypergammaglobulinæmia" in 11 of 57 relatives from 18 families of patients with S.L.E.; and Rodnan et al.[9] found definite hypergammaglobulinæmia in 12 of 59 relatives, thus confirming the observations of Larsson and Leonhardt.

9. Rodnan, G. P., Maclachlan, M. J., Creighton, A. S. *Clin. Res.* 1960, 8, 197.

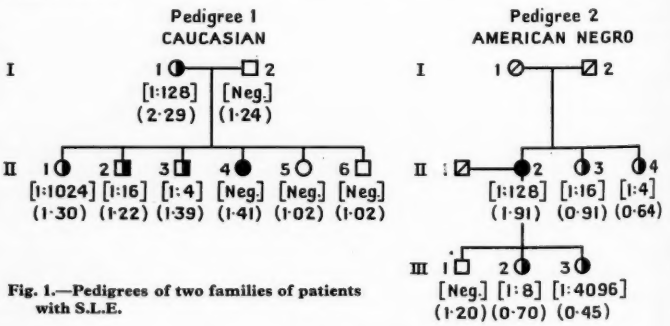

Fig. 1.—Pedigrees of two families of patients with S.L.E.

● =S.L.E.
◑ =positive test for antinuclear factors.
○ =negative test for antinuclear factors.
⊘ =not tested.
[ ] =titre of antinuclear factors.
( ) =serum-γ-globulin (g. per 100 ml.).

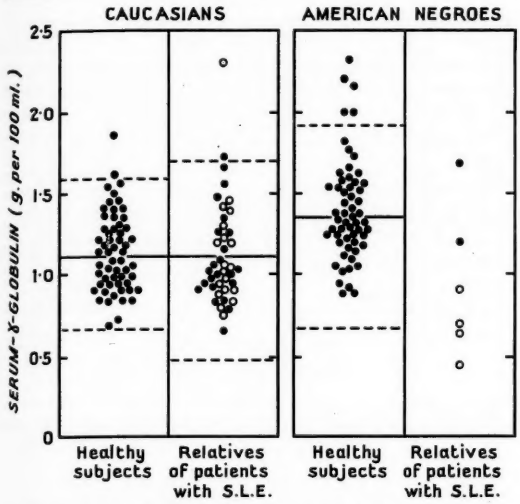

Fig. 2.—Serum-γ-globulin levels in healthy subjects and in relatives of patients with S.L.E.

The mean values are given by continuous lines and two standard deviations by interrupted lines.

o = patients with positive tests for antinuclear factors.
• = patients with negative tests for antinuclear factors.

We found few relatives with hypergammaglobulinæmia, but somewhat high γ-globulin levels were found in 5 of 7 members of pedigree 1. Unusually low γ-globulin levels were found in 4 of 5 members of pedigree 2. This finding is of interest in view of the reported development of an arthritis resembling rheumatoid arthritis in almost half of 16 children with the congenital form of agammaglobulinæmia, and of collagen disease in patients with congenital and acquired agammaglobulinæmia.[10]

The most striking abnormality found was the high prevalence of positive tests for antinuclear factors in the serum of relatives of patients with S.L.E. The results strongly suggest that an abnormal protein or proteins with an affinity for cell nuclei in vitro are present in the serum of about half the relatives. By contrast, positive tests for antinuclear factors were found in the serum of only 1 of 50 subjects with diseases unrelated to S.L.E. and in none of the 40 healthy subjects studied. Hargraves' cells have been reported in about 12% of patients with rheumatoid arthritis [11] and occasionally in other so-called collagen diseases. We found positive tests for antinuclear factors in the serum of only 5 of 35 patients with these disorders. Thus the prevalence of positive tests for antinuclear factors was considerably higher in relatives of patients with S.L.E. than in patients with rheumatoid arthritis, scleroderma, and dermatomyositis. As rheumatoid arthritis and positive serological tests for rheumatoid factor appear to be commoner in relatives of patients with S.L.E. that in the general population,[8 9] relatives of patients with S.L.E. may possibly comprise at least a proportion of the patients with clinical rheumatoid arthritis and positive Hargraves' cells or antinuclear factors.

The ætiology of systemic lupus erythematosus is still unknown. In recent years abundant evidence has been accumulated that the serum of patients with S.L.E. contains several abnormal γ-globulins. These abnormal γ-globulins, which react with cells or cell constituents in vitro, can probably be classified as auto-immune antibodies. Patients with S.L.E. also show increased responsiveness to foreign antigens.[12] The mechanism underlying the appearance of autoimmune antibodies and the increased sensitivity to foreign antigens is still poorly understood. Both these abnormalities, however, point to a derangement in the system regulating "immunological homœstasis". The data reported here indicate that this derangement probably has an hereditary basis, and suggest that overt disease may result from exposure to various antigens and other provocative stimuli in persons with the appropriate hereditary abnormality in the homœstasis of the antibody-producing system.

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BLOOD-GROUP DISTRIBUTION IN MEGALOBLASTIC ANÆMIA OF PREGNANCY

FOLIC-ACID deficiency in pregnancy is characterised by the appearance of megaloblasts in the marrow. In the most severe cases these are of the classical Ehrlich type, as seen in addisonian anæmia, whereas transitional megaloblasts are encountered in the milder forms of the disease. More recent studies have shown that folic-acid depletion frequently occurs in late pregnancy without producing megaloblastic changes in the marrow,[13] although the hæmoglobin-level can generally be raised by the administration of folic acid.[14]

Folic-acid deficiency in pregnancy can thus be conveniently classified in four categories:

Grade 0.—The marrow remains entirely normoblastic and folic-acid depletion can be diagnosed with certainty only by folic-acid assays. In these cases the hæmoglobin level can usually be raised by folic-acid therapy.

Grade 1.—The mildest form of megaloblastic anæmia, in which the marrow is predominantly normoblastic, though it contains a number of transitional megaloblasts. Diagnosis in such cases may need confirmation by other criteria—e.g., a raised serum-iron level and satisfactory response to folic-acid therapy.

Grade 2.—The marrow is predominantly megaloblastic, but the majority of cells is of the transitional type.

Grade 3.—A florid megaloblastic marrow in which the classical Ehrlich type of megaloblast predominates. The marrow picture in these cases is indistinguishable from that seen in addisonian anæmia.

Obviously, the marrow-changes in these four categories reflect, to some extent, the degree of folic-acid depletion in any given person. It would be an oversimplification to assume from this that all pregnant women with folic-acid

10. Gitlin, D., Gross, P. A. M., Janeway, C. A. *New Engl. J. Med.* 1960, **260**, 72.
11. Friedman, I. A., Sickley, J. E., Poske, R. M., Black, A., Bronsky, D., Hartz, W. H. Jr., Feldhake, C., Reeder, P. S., Katz, E. M. *Ann. intern. Med.* 1957, **46**, 1113.

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12. Holman, H. R. *Ann. Rev. Med.* 1960, **11**, 231.
13. Chanarin, I., MacGibbon, B. M., O'Sullivan, W. J., Mollin, D. L. *Lancet*, 1959, ii, 634.
14. Giles, C., Burton, H. *Brit. med. J.* 1960, ii, 636.

deficiency are equally liable to develop advanced megaloblastic anæmia. A study of the blood-group distribution of patients with megaloblastic anæmia of pregnancy has shown that cases with a grade-3 type of marrow, in which the classical Ehrlich type of megaloblasts are encountered, probably represent a special group which appears to be genetically determined.

The blood-group distribution of 175 patients with megaloblastic anæmia of pregnancy was compared with that of 3500 routine antenatal cases in the same district. As seen in table I, the only deviation from the norm is an increase in the incidence of blood-group A in patients with megaloblastic anæmia, but this is less than the group A preponderance reported in addisonian anæmia.[15]

TABLE I—BLOOD-GROUP DISTRIBUTION IN MEGALOBLASTIC ANÆMIA OF PREGNANCY

Blood group	Routine antenatal (3500 cases)	Megaloblastic anæmia of pregnancy			
		All grades (175 cases)	grade 3 (77 cases)	grade 2 (59 cases)	grade 1 (39 cases)
O	46%	43%	34%	48%	56%
A	42%	50%	60%	46%	36%
B	9%	5%	5%	3%	5%
AB	3%	2%	1%	3%	3%

When, however, cases of megaloblastic anæmia of pregnancy were classified according to their hæmatological grade (from 1 to 3), and the blood-group distribution calculated separately for each grade, it became obvious that there was only one category with a definite group-A preponderance—namely, grade 3—composed of those cases in which the marrow most closely resembles that of addisonian anæmia. Table I shows that the incidence of blood-group A in 77 cases in category 3 is 60%, compared with a proportion of 42% in the controls. As seen in table II, this difference is statistically significant ($P < 0.01$). On the other hand, the group-A incidence in those patients who were classified in grades 1 and 2 is 42%, which closely approaches the normal distribution.

TABLE II—INCIDENCE OF GROUP-A IN MEGALOBLASTIC ANÆMIA OF PREGNANCY

Megaloblastic anæmia of pregnancy	Number of cases	Group A incidence	χ^2	P
All grades	175	50%	4·18	<0·05
Grade 3	77	60%	9·16	<0·01
Grade 2	59	46%	0·30	>0·5
Grade 1	39	36%	0·43	>0·5
Grades 1 and 2 ..	98	42%	0·04	>0·5
Controls	3500	42%		

Analysis of clinical and hæmatological findings in women with the various grades of megaloblastic anæmia shows that grade-3 cases tend to present with more severe anæmia, higher serum-iron levels, and usually show a greater reticulocyte response to folic-acid therapy. In other respects, patients in the various categories do not appear to differ. Their age-distribution is similar and the incidence of achlorhydria is approximately the same. A history of an inadequate diet in pregnancy appears with equal frequency in all categories, and the previous administration of iron does not seem to affect the marrow-picture. Gastrointestinal symptoms, especially anorexia and ulceration of the mouth, occur equally often with lesser degrees of megaloblastosis.

It would obviously be premature to draw definite conclusions from the blood-group distribution in a single series of cases from one district. These findings suggest, however, that while folic-acid deficiency, with or without megaloblastic changes in the marrow, is a frequent occurrence in late pregnancy, patients with advanced megaloblastic anæmia constitute a special group in which there is an inherited predisposition to the disease. The report by Giles and Burton[14] of 13 out of 41 cases of megaloblastic anæmia of pregnancy, with evidence of diminished fat absorption, has already pointed to a constitutional factor in the ætiology of the disease. It is perhaps significant that a grade-3 type of marrow was found in 10 of these 13 cases.

15. Fraser Roberts, J. A. *Brit. med Bull.* 1959, **15**, 129.

My thanks are due to Mr. A. H. Iliffe, of the University College of North Staffordshire, for the statistical analysis; to Dr. R. B. McConnell for his helpful advice; to Dr. A. J. McCall for his help and encouragement; and to the research fund of the Birmingham Regional Hospital Board for its assistance.

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New Inventions

A HEART-LUNG MACHINE FOR INFANTS AND YOUNG CHILDREN

MOST heart-lung machines are designed for patients of 3 to 5 years and over. Moreover, particular attention has been directed towards apparatus capable of maintaining the circulation in full-sized adults. A number of congenital defects are responsible for death within the first year of life [1]; but existing machines, with their relatively large priming volume, are not readily adaptable to the low flows and blood-volumes in this age-group.

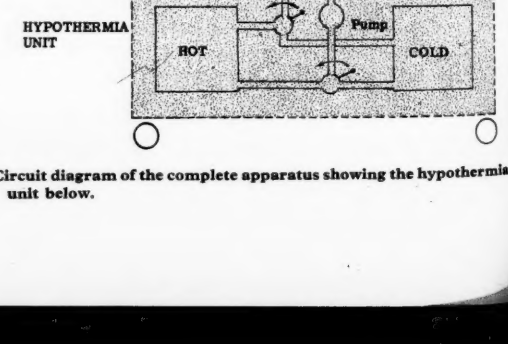
The following heart-lung circuit has been designed to provide flows up to 1·2 litres per min., with a priming volume of 500–750 ml.

Apparatus

Basically this is a scaled-down version of the model in current clinical use.[2] The oxygenator is of the rotating disc variety, and a heat-exchanger is included in the circuit. The apparatus is entirely self-contained, being provided with its own source of heating and cooling fluids (see figure).

Two complete oxygenators are available (22 and 34 cm. long). The smaller provides for flows up to 700 ml. per min., and the larger for flows up to 1200 ml. per min. The discs are of stainless steel, 7·8 cm. in diameter and spaced 4 mm. apart. Spacing of the discs at less than 4 mm. causes foaming. No silicone or anti-foam is required in the oxygenator. The rotation speed of the discs is 120 r.p.m.

1. Bonham-Carter, R. E., Waterston, D. J. *Brit. Heart J.* 1957, **19**, 589.
2. Ross, D. N. *Brit. med. J.* 1960, ii, 571.



Circuit diagram of the complete apparatus showing the hypothermia unit below.

Cooling and rewarming is by means of a heat-exchanger constructed from stainless steel. A filter and bubble trap are incorporated in the arterial outflow line. Two sucker lines are provided which deliver their blood on to five perforated plates lightly coated with anti-foam. The output of the arterial pump and of the pump controlling the suction lines can be varied by two simple hand controls. The apparatus and tubing in contact with blood is sterilised in ethylene oxide for 24 hours before use.

The hypothermic and heating equipment is contained within a low trolley which acts as a mount for the heart-lung machine. In this way the apparatus, while remaining compact, is entirely self-contained. The cold source is supplied with a mixture of ice and water kept in a lagged 2 gal. tank, and hot water is kept thermostatically controlled at about 40°C in a separate tank.

Application

The apparatus has been used in twenty-five dog experiments. In addition, four children have been operated on, with one death. In use the machine requires very little adjustment, the running being in the hands of one technician.

The apparatus has been constructed for me by Mr. A. F. Turner in the Guy's Hospital Medical School workshop, and it will be available through Cardiac Recorders, Ltd., Weymouth Street, London, W.1.

Guy's Hospital, London, S.E.1

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Reviews of Books

Medical and Dental Aspects of Fluoridation

W. A. CANNELL, M.R.C.S., D.P.H., L.D.S. London: Lewis. 1960. Pp. 125. 15*s*.

MOST of the growing literature of fluoridation and fluorine is scattered in various journals. A great deal of the research has been done in the United States, and the few books that have appeared since Roholm's classic text in 1937 have been published there. A British survey of the present state of knowledge is welcome, and Dr. Cannell gives a concise and readable summary, with an account of some important original work on the effect of trace elements.

It is a relief to find a book that deliberately does not discuss the various fluoridation trials in the United States. So much has been written about them and their real and alleged shortcomings that there is a risk of losing sight of one of the fundamental issues—the physiological and biochemical effects of fluorides. Too little is generally known about the systemic effects of fluorides, and Dr. Cannell's book should go a long way towards dispelling this ignorance, especially among the opponents of fluoridation.

The chapters on the pharmacology of the fluorides and on the calcification of skeletal and dental tissues are particularly good. Speculation is kept to a minimum, and the facts are presented fairly, and without bias. Not everyone will agree with Dr. Cannell in his excursion into the field of logical causality (p. 69), but the inescapability of fluorides renders his argument an attractive one.

The final chapter, on the public-health aspects, puts forward a well-reasoned case for the fluoridation of water-supplies. Other possible means of administration are discussed in the light of recent research. The bibliography is comprehensive and up to date, though there is no reference to Mackenzie's extensive review.[1]

This is probably one of the best accounts of fluorides and their effects that has been published for some time.

Pathology of Infancy and Childhood

AGNES R. MACGREGOR, M.D., F.R.C.P.E., F.R.C.O.G., reader in pathology, Edinburgh University. Edinburgh and London: E. & S. Livingstone. 1960. Pp. 631. 75*s*.

A VOLUME concerned entirely with pædiatric pathology has been urgently needed by many pathologists, and the gap has been partly filled by this book in which Dr. Macgregor incorporates the experience of her many years as an authority on this subject. It is a simple book: it makes no pretension to being a work of reference for pædiatric pathologists, but has been designed for the pathologist whose main work and interests are with older patients. Most conditions which he is likely to meet are considered adequately, with proper regard for their relative importance and incidence. Bearing in mind that the great majority of necropsies are on infants dying in the perinatal period, notes on necropsy technique and detailed practical accounts of perinatal conditions are included. Many facts in this part of the book rarely appear in print and are usually appreciated only after considerable experience. The section dealing with developmental anomalies could have been fortified by the inclusion of notes on embryology, supported by diagrams. Since many hospitals have cardiothoracic units, and deaths from cardiovascular anomalies often form a big part of pædiatric necropsy work, the account of these anomalies may be too superficial. Although the photographs of specimens of malformed hearts are generally self-explanatory, a few diagrams would have enhanced clarity. A lack of uniformity between different sections of the book is mainly due to the omission of conditions which are not peculiar to infants or children, or which are well described in standard textbooks of pathology. But a few relatively important diseases are treated rather briefly, and many less common conditions are not mentioned even by reference to the literature. Although the references are well chosen and up to date, the bibliography will be little help to the pathologist faced with an unusual case.

This book will be particularly useful to those embarking upon a career in pathology or pædiatrics. Its value to the established pathologist is limited, but it will be enjoyed by those who appreciate the signs of the author's wide experience.

The Chemical Senses in Health and Disease

H. KALMUS, SC.D., M.D., reader in biology, University of London; S. J. HUBBARD, B.SC., PH.D., lecturer in physiology, University College, London. Springfield, Ill.: Charles. C. Thomas. Oxford: Blackwell Scientific Publications. 1960. Pp. 95. 30*s*.

NO disciple of Brillat-Savarin needs to be reminded of the importance of the chemical senses—concerned as they are with taste and smell. But many may be surprised at the complexity of the physiological processes subserving the art of transcendental gastronomy. Who would have suspected, for instance, that over 60 volatile substances contribute to the aroma of coffee? This suggests almost endless permutation of naturally occurring odours: and many kinds of odour-receptors. On the other hand, only four basic tastes—sour, salt, sweet, and bitter—are firmly established. The interplay of taste and smell, the importance of these chemical senses in behaviour both in animals and man, some curious and interesting genetical variations in both senses, and lines of future research and their practical importance are all discussed in this book. The psychological aspects—in some ways the most fascinating of any—are also briefly mentioned. The book is short and well worth the attention of physiologist and clinician. It is a pity the price is so high.

The Early History of Surgery

W. J. BISHOP, editor, *Medical History*. London: Robert Hale. 1960. Pp. 192. 18*s*.

AT a time when road travel is becoming increasingly dangerous, it is good to discover that some at least of its former hazards have been mitigated. Richard Wiseman, writing in 1676, described the misadventure which befell "a gentleman of about thirty years of age, who was coming out of Hertfordshire through Tottenham and riding upon the causeway near an inn when, one emptying a chamber pot out of the window

1. Mackenzie, E. F. W. *Lancet*, 1952, i, 961.

as he was passing by, his horse started and rushed violently between a signpost and a tree which supported part of the sign. The poor gentleman was beaten off his horse and lay stunned upon the ground". This case, and Wiseman's successful management of it, is one of the many which Mr. Bishop uses to illustrate the evolution of surgery. His book is happily written in a style easily intelligible to the layman, yet technical enough to appeal to doctors as well; and, as might be expected from the author's status as an antiquarian, it is distinguished by a meticulous attention to accuracy. Even in such a matter as the emergency operation on King Edward VII, it is noted that it was never officially stated whether or not an appendicectomy had been performed.

The Healthy Child

His Physical, Psychological, and Social Development. Editors: HAROLD C. STUART, M.D., emeritus professor of maternal and child health, Harvard University School of Public Health; DANE G. PRUGH, M.D., associate professor of pædiatrics and psychiatry, University of Rochester School of Medicine and Dentistry. Cambridge, Mass.: Harvard University Press. London: Oxford University Press. 1960. Pp. 507. 80*s*.

THIS book is written for all who work professionally with children, whether in the areas of medicine, education, social work, public health, nutrition, nursing, or psychology; and those who have contributed to it come from a correspondingly wide range of disciplines. The emphasis is on "healthy development" and how it may best be protected or promoted. The book presents in broad terms a picture of the child and his expected progress from conception to maturity. It is concerned with him as an individual who is changing or developing according to natural laws and inborn potentialities. It deals with the major aspects of his physical development and also with his psychosocial development and the factors which favour mental health. Among its many interesting chapters is one on emotional changes in pregnancy. Emphasising throughout the wide range of normal, the book is a valuable contribution to the increasing literature on the important subject of normality.

Life's Long Journey

KENNETH WALKER, F.R.C.S. London: Victor Gollancz. 1960. Pp. 191. 21*s*.

Mr. Kenneth Walker writes, for the general public, to discount excessive claims for the material sciences in general, and in particular the supposition that natural selection sufficiently explains the course of human evolution and that scientific control could or should direct its future course, if any.

In the earlier chapters he seems to postulate "life" as a forward-looking entity planning its own development; but throughout the book "Nature", without inverted commas, appears as experimenter and giver or withholder of gifts, and it is not at all clear whom or what he regards as the "eternal mover", though he makes a firm claim for the life spiritual and the reality of mystical experience.

Like some others, Mr. Walker regards the present population explosion as more dangerous to humanity than the atom bomb and fears our despairing recourse to Communist termitism. He is surely unjust to Ecclesiastes ("cast thy bread upon the waters") in ascribing to him and not to Proverbs the advice to look to the ant for exemplar; but that, in the present human predicament, the termitary is terrifying to contemplate is sure enough.

No Crying in this Cradle

The Expectant and Nursing Mother's Bedside Book. ELIZABETH G. MORRISON, S.R.N., S.C.M., M.T.S.; JOAN GOLDMAN. London: Ernest Benn. 1960. Pp. 159. 15*s*.

Elizabeth Morrison has had a vast experience of reading and answering letters from mothers because for thirty years she has run the correspondence columns in *Nursery World*. But one wonders just how much practical experience she has had, and how recently. Some of the advice she gives is outdated—e.g., "it is advisable to go specially easy on meat in the last month or two of pregnancy". There seems little point in advising an expectant mother not to eat mixed grill and telling her that it won't make her or the baby "feel too good". The book says that eiderdowns for babies "ought to be forbidden by an Act of Parliament", not because they may smother the baby, but because "nothing more effective exists to make the baby sweat". Most of the book is an invective in favour of breast-feeding. But the reasons why babies should be breast-fed whenever possible are poorly argued and unconvincing. It is true that some doctors do not know much about normal babies, but it is doubtful whether many are as woefully ignorant as this book suggests. Doubtless dissatisfied patients write in sorrow and anger to the magazines, and Sister Morrison must receive many such letters. But to describe the doctor and baby clinic as "statistics-ridden prophets" who "yell the roof off with their denunciations" seems to be going rather far.

Nevertheless, the book contains a good deal of sensible, practical advice of the kind that is being given daily by good doctors and nurses up and down the country.

Clinical Bacteriology (2nd ed. London: Edward Arnold. 1960. Pp. 309. 30*s*.).—The duties of the bacteriologist in a hospital are to isolate pathogenic bacteria, to decide from collateral evidence and probability that these have some connection with the patient's illness, and—a recent development—to give guidance on the treatment of the infection to those responsible for the patient. The identity of the organism is not vastly important (except to the epidemiologist) but custom at least demands that this shall be reported as accurately as possible. It is this academic pride in going beyond the bare diagnosis and treatment which distinguishes the medical bacteriologist from the technician. When Dr. Joan Stokes' book first appeared it was the best benchbook for the medical bacteriologist which had been published and it remains so today. The academic background (for which she still apologises) converts what might have been a mere cookery book into a readable and reliable guide to work at the bench. The changes in this second edition add some new methods and take account of some recent advances in knowledge, but as before it is clear that all the recommendations are made in the light of personal experience.

Demonstrations of Physical Signs in Clinical Surgery (13th ed. Bristol: John Wright. 1960. Pp. 928. 75*s*.).—In 1927 medical illustration was just emerging from the era of line drawings. Some textbooks contained a few photographs, but they were often reproduced in poorly contrasting shades of grey, and the technique of colour printing was in its infancy. When, therefore, in that year, the first edition of this book appeared, with its clear and vivid illustrations, students were quick to appreciate the efforts that Mr. Hamilton Bailey and his publishers had made on their behalf. It comes as no surprise to learn that, of the English editions alone, 177,000 copies have now been sold. The latest edition contains more than four times as many pages and illustrations as the first, and if this growth-rate is maintained the twenty-fifth edition may well include an illustration of the typical lesion the volume produces by resting on the reader's knees. Many pictures have been furnished by distinguished clinicians, some of whom would no doubt acknowledge that they were helped to their first academic successes by the very work to which they have now contributed.

Principles of Orthopædic Surgery. (London: J. & A. Churchill. 1960. Pp. 799. 150*s*.).—Dr. Paul E. Colonna earlier published a book based on his lectures and teaching-rounds at the University of Pennsylvania. This volume is an expanded form (a notable difference is the increased space devoted to traumatic lesions) but has in common with the earlier one a style of writing and printing that makes for easy reading even over long periods. A few of the radiographs are not adequately reproduced, but the work is one of the very few which can be freely quoted on either side of the Atlantic without modification and with equal authority.

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Malaria Research

WHEN LAVERAN discovered the malaria parasite in 1880 he opened the flood gates to a torrent of research which, despite ebbs and flows, today runs as strongly as ever. It seemed at various times that the problems of malaria had been finally solved: at the end of the century when the mechanism of transmission through mosquitoes was worked out, the way seemed open (or so at least Ross thought) for the control and abolition of the disease; in the years between the wars, and later, a range of drugs was synthesised which seemed to offer the perfect therapy; then the researches on the exo-erythrocytic cycle from 1936 onwards had apparently filled the last gap in our knowledge of the life-cycle of the parasite, while the discovery of dicophane (D.D.T.) and other residual insecticides was thought to have provided the final answer to the problem of mosquito eradication. And today, although we may feel that the end is in sight, this impression may be as false as any similar one expressed earlier in the century.

The study of malaria involves so many disciplines that a special composite science—malariology—inevitably developed, with its own institutes, journals, techniques, jargon, and specially its cadre of international workers who have devoted their lives to this fascinating borderline of research. The malariologist must be prepared to dabble in entomology and protozoology, in clinical medicine, in chemotherapy and biochemistry, in statistics and genetics, even in such uncongenial subjects as engineering, administration, and sociology. An issue of the *Bulletin of the World Health Organisation* [1] illustrates something of this range. It includes a paper by Sir GORDON COVELL (who has been awarded the Walter Reed medal for services to tropical medicine) on the potential danger of apyrexial carriers of malaria in constituting an unobvious reservoir of infection during eradication campaigns; an account by A. S. ALVING (Chicago) of a new method of administering primaquine (the drug which destroys the exo-erythrocytic stages of the malaria parasite and prevents relapses) by reducing the toxicity of this invaluable drug; a complete analysis by L. T. BRUCE-CHWATT and C. GÖCKEL, of W.H.O., of the results of precipitin tests (carried out by B. WEITZ, of the Lister Institute) of the stomach contents of anopheline mosquitoes, which showed that 48 out of 51 species fed to a greater or lesser extent on human blood; and other papers dealing with the action of dicophane and other residual insecticides. R. C. MUIRHEAD-THOMSON, and G. SACCA and Y. GUY show how mosquitoes alter their habits after long exposure to dicophane—the so-called "behaviouristic resistance". The Colonial Pesticides Research Unit at Arusha suggests that the addition of a resin (ceredor) to gamma benzene hexachloride has provided the ideal insecticide for malaria control.

Current research in malariology is as eclectic as ever. Fundamental studies on the life-cycle of the parasite have been facilitated by using chimpanzees instead of volunteers; and BRAY [2] in Liberia, after finding that the liver of this ape is as susceptible as that of man to *Plasmodium vivax*, *ovale*, and *falciparum*, successfully demonstrated for the first time the tissue stages of the quartan parasite (*P. malariæ*) by this technique. There has been much controversy over the nature of nuclear division in malaria parasites, but BANO [3] has clearly demonstrated that the first division of the nucleus of the oocyst is meiotic, and that subsequent ones are mitotic, with a characteristic number of chromosomes in each of the seven species of plasmodia she studied. The protective action of sickle-cell hæmoglobin against *P. falciparum* was demonstrated by ALLISON [4] and other workers in 1954 and later. More recently GILLES et al.[5] have suggested that the possession of another hereditary trait—glucose-6-phosphate-dehydrogenase deficiency in red blood-cells—also has an inhibitory effect on the parasite.

Research on resistance has made much progress in the past few years. In Algiers, SERGENT and PONCET [6] studied the development of resistance against chloroquine by *P. berghei* in rats and mice, and introduced the term "mithridatism" for this feature. The work of BISHOP [7] at the Molteno Institute went deeper and indicates that the resistance may have a mutational origin and be concerned with the metabolism of *p*-aminobenzoic acid and folic acid. The resistance of several species of mosquitoes to insecticides presents a baffling problem in the eradication programme; and the genetic nature of this phenomenon has been shown at the Ross Institute, where DAVIDSON and JACKSON [8] demonstrated that resistance was of two independent types—to dicophane and dieldrin respectively, arising from single genetic factors, recessive in the former and semidominant in the latter, and applying to species of anopheline mosquitoes from as far apart as Africa, Indonesia, Iraq, and Central America. This work has been confirmed to some extent by the cytological studies of FRIZZI and others [9] in Pavia; they have described in great detail the chromosome pattern of several species of mosquitoes, including susceptible and resistant forms. These profound laboratory investigations stemmed

1. *Bull. Wld Hlth Org.* 1960, **22**, no. 6.

2. Bray, R. S. *Brit. med. J.* 1959, ii, 679.
3. Bano, L. *Parasitology*, 1959, **49**, 559.
4. Allison, A. C. *Brit. med. J.* 1954, i, 290.
5. Gilles, H. M., Watson-Williams, J., Taylor, B. S. *Nature, Lond.* 1960, **185**, 257.
6. Sergent, E., Poncet, A. *Arch. Inst. Pasteur Algérie*, 1959, **37**, 227.
7. Bishop, A. *Biol. Rev.* 1959, **34**, 445.
8. Davidson, G., Jackson, C. E. *Nature, Lond.* (in the press).
9. D'Alessandro, G., Frizzi, G., Mariand, M. *Bull. Wld Hlth Org.* 1957, **16**, 859.

directly from observations made in the field in Sokotu, Northern Nigeria, where RAMAKRISHNAN and ELLIOTT [10] noticed the sudden resistance to dieldrin of *Anopheles gambiæ*. This is a good example of "incidental research", which has been a feature of malariology throughout its history.

Animal malaria, which has excited interest from the earliest days, has attracted fresh attention through the discovery [11] in the U.S.A. that a strain of monkey malaria, isolated in London, readily infects man. The parasite was named after G. BASTIANELLI, the last of the great band of Italian malariologists, who died last year at the age of 96. This organism was being studied in three laboratories in the U.S.A.; and, in all three, accidental infections occurred through the bites of infected mosquitoes. The disease proved to be mild, and clinically and parasitologically resembled benign tertian malaria. Subsequently G. R. COATNEY, D. E. EYLES, M. E. GETZ, and H. K. BEYE transmitted the infection back to monkeys and to volunteers, both by mosquitoes and by inoculation of blood containing parasites. It was at once realised that here at last was direct evidence that monkeys might act as a reservoir of malaria in Nature, and that this infection might constitute a zoonosis. Previously it had been well established [12] that another monkey parasite—*P. knowlesi*—could easily affect man in its blood form, but mosquito transmission of this parasite to man has not yet been achieved; other simian parasites, such as *P. malariæ* of chimpanzees and *P. hylobati* of gibbons, are also suspected but not proved to be zoonoses. *P. cynomolgi bastianellii* (as this latest parasite is called) originated from a crab-eating monkey (*Macaca irus*) captured in Pahang, and the next stage of the research will be to discover first how many (if any) of the local inhabitants of this forested region are infected with the parasite, and secondly how widely it is distributed in the East Indies, Thailand, and the Far East. With such a monkey reservoir of malaria, eradication may be an even more difficult undertaking than it seems at present; but, until the situation has been investigated fully, the extent of the danger cannot be assessed. It may even be found that the parasite does not exist in Nature, but was the result of one of the flagrantly unnatural processes to which the parent strain had been subjected: it was originally contaminated in both sexual and asexual forms with *P. knowlesi* [13]; it was flown across the Atlantic in iced blood; and it was maintained in a variety of exotic mosquitoes very different from its original insect vector.

If malaria is to be eradicated from the world, these and other problems will have to be solved. Even then the subject of malariology will not be extinguished, because much remains unknown about the malaria of lizards and birds, rats and lemurs, and bats and antelopes; and, though their parasites do not appear to affect man, the zoologist will be impelled to investigate them further, with their attendant insect hosts.

10. Elliott, R., Ramakrishnan, V. *Nature, Lond.* 1956, **177**, 532.
11. Eyles, D. E., Coatney, G. R., Getz, M. E. *Science*, 1960, **131**, 1812.
12. Ciuca, M. Editura. *Acad. Rep. pop. Romini*, 1955.
13. Hawking, F., Mellanby, H., Terry, R. J., Webber, W. A. F. *Trans. R. Soc. trop. Med. Hyg.* 1957, **51**, 397.

The Mongol Chromosome and Some Others

THE spate of new observations on human chromosome anomalies continues, and it seems worth following our recent attempt to survey the X chromosome disorders [1] with a similar account of one of the autosomes.

Anomalies of the "mongol" chromosome (no. 21 on the Denver system [2]) have been most studied: indeed, apart from the sex chromosomes, this is the only one that can yet be associated in any but the most tentative way with a definite clinical syndrome. Classical mongolism has now been shown beyond dispute to be caused by an extra chromosome, no. 21.[3–5] "Caused by", we would repeat: though we do not know how the effect is produced, the relation is too strong to shelter behind the circumlocutory hedging implicit in the words "associated with". The production of "trisomy" of this kind, with three apparently normal chromosomes instead of the normal pair, by the process of non-disjunction during formation of the gamete, the effect of age on the incidence of non-disjunction, and the consequent explanation of the influence of maternal age on the incidence of mongolism are now familiar themes. Interest is concentrating on certain cases in which the effect of trisomy-21 is produced by something other than the usual mechanism. Such cases have been sought where youth of the mother, or (more certainly) evidence of familial transmission, has suggested that the ordinary non-disjunction mechanism has not been at work. The first of these was reported by POLANI et al.[6] earlier this year. A mongol girl, one of a number examined because their mothers were much younger than usual at the time of their birth, was found to have the normal total number of 46 chromosomes. One chromosome of the very characteristic medium-sized acrocentric group (nos. 13–15, the "wishbones") was missing, and instead there was an atypical larger chromosome. Ingeniously and most plausibly, POLANI et al. accounted for this by assuming that the patient had a third no. 21 present (thus accounting for her mongolism) but that this had fused with the missing no. 14 (or thereabouts) to give the abnormal larger chromosome. ("Fusion" oversimplifies the process, which is probably one of translocation, with exchange of material between two chromosomes: if in this process a large fragment of one chromosome is exchanged for a small fragment of another, the result will be a large chromosome carrying most of the material of both and a small one carrying much less. When these are separated in the process of gamete formation, imbalance will clearly result.)

More recently PENROSE et al.[7] have reported further "translocation" mongols. One was much like the first, except that the extra no. 21 was apparently joined to no. 22 instead of no. 14. In addition, they reported a

1. *Lancet*, July 23, 1960, p. 191.
2. *ibid.* 1960, i, 1063.
3. Lejeune, J., Gautier, M., Turpin, R. *C.R. Acad. Sci., Paris*, 1959, **248**, 602.
4. Jacobs, P. A., Baikie, A. G., Court-Brown, W. M., Strong, J. A. *Lancet*, 1959, i, 710.
5. Böök, J. A., Fraccaro, M., Lindstern, J. *Acta pædiat., Stockh.*, 1959, **48**, 453.
6. Polani, P. E., Briggs, J. H., Ford, C. E., Clarke, C. M., Berg, J. M. *Lancet*, 1960, i, 721.
7. Penrose, L. S., Ellis, J. R., Delhanty, J. D. A. *ibid.* Aug. 20, 1960 p. 409.

most remarkable family. Two mongol sibs each had 46 chromosomes, with the same 21/15 translocation-fusion to account for it. In addition, three normal female relatives were found to have 45 chromosomes only. In them an essentially normal chromosome complement had apparently been affected by the " fusion " of one chromosome each from the pairs 15 and 21. In this family the translocation had obviously occurred at least in the great-grandparents. The mere joining together of two chromosomes had no recognisable effect, but the tendency to imbalance during gamete formation inseparable from this fusion gave rise to some offspring with too much chromosomal material, who were the mongols. The importance of this form of transmission has been established by the description of a very similar but even larger family group by CARTER et al.[8] The mechanism is fairly easy to follow from the diagram (fig. 4) of POLANI et al.[6]

Another remarkable family was reported by FRACCARO et al.[9] Here the mongol patient had 46 chromosomes, and an abnormality of the smaller chromosomes which was thought at first to represent the ordinary mongol trisomy of no. 21, with translocatory pseudo-fusion of two of the three to produce an abnormal single larger chromosome. His father, who appeared perfectly normal and is a minister of religion (and who may thus be the first exception to the rule that chromosomal anomalies and university degrees are incompatible) was found to have 47 chromosomes and to be trisomic for no. 19. The findings in this family admit of no simple explanation with our present knowledge, unless indeed (as seems unlikely) the diagnosis of the child as a mongol is at fault. But clearly we must expect some strange findings from the systematic examination of familial mongols. There are rumours of yet other variants on the way.

Anomalies of other chromosomes form a much more confusing picture. Trisomies of no. 17 [10] and of one of the 13–15 group [11] seem well established. Trisomy of no. 22 is also not unlikely,[12] though identification of the chromosome present is not very certain (might it even have been an extra Y?) and its relation to the Sturge-Weber syndrome present cannot yet be accepted confidently. Trisomy of no. 11 [13] and of no. 6 [14] have both been claimed, but both cases had the double sex chromatin characteristic of the XXX syndrome,[15–17] and, as we [1] and others [18] have already suggested for the first of these, these may well both be examples of the XXX syndrome with perhaps minor irregularities of one of the X chromosomes concerned. Multiple trisomies have also been reported,[19 20] the most striking being FRACCARO et al.'s case [21] with 49 chromosomes altogether (nos. 8 and 11 trisomic, plus XXY); and indeed, except for the viability of the patients, there is nothing incredible about this, for the conditions which cause non-disjunction of one chromosome pair could quite reasonably be supposed equally to affect others. Perhaps the most nearly incredible of all the findings is the demonstration by BÖÖK and SANTESSON [22] of trisomy of every chromosome pair, giving a triploid individual with 69 chromosomes.

It is too early to hope to decipher the pattern which must lie behind the varied clinical manifestations of these anomalies. The sex-chromosome disorders present at least some trace of logic; and mongolism, though we have no glimmer of hint as to the mechanism by which the chromosome defect produces its highly specific effects, presents at least a consistent pattern. Of the others hardly any two cases are sufficiently alike for conclusions to be possible. It seems not unlikely that there will be found to be some non-specific tendency to congenital anomalies related more to the amount than to the nature of the chromosomal anomaly (mental defect being the most constant element), and a first task will be the identification, behind this screen, of more specific patterns related to disorders of individual chromosomes.

The demonstration in viable children of triploidy [22] or trisomy of three large chromosomes [21] at one end of the scale, and in normal individuals of trisomy [9] or translocations [7 8] at the other, shows that the human organism is not as sensitive to such changes as was once supposed. Every one of the twelve chromosome pairs of that old friend of the materia medica, *Datura stramonium*,[23] can exist in a trisomic form, and every one has its characteristic phenotype, or, as one calls it in medicine, its characteristic clinical syndrome. Perhaps we will soon recognise equally characteristic syndromes for each of our own twenty-two autosome pairs.

Tumours of the Bladder

IN the past decade the causes, treatment, and prevention of bladder tumours have aroused much interest. Fascinating questions surround the incidence of this disease. Why is it increasing in younger males? Why is it apparently commoner in towns than in the country? Why is it rare in Japan and India? Now that β-naphthylamine is no longer employed in the dye, chemical, or rubber industry, which industries still use carcinogens such as benzidine?

A possible cause of bladder tumours is the excretion in the urine of an abnormal metabolite of tryptophane. Some biochemists believe that this metabolite is hydroxykynurenin, others that it is hydroxyanthranilic acid or an allied compound. These chemicals can be suppressed in at least three ways: by administering

8. Carter, C. O., Hamerton, J. L., Polani, P. E., Gunalp, A., Weller, S. D. V. *ibid.* Sept. 24, 1960, p. 678.
9. Fraccaro, M., Kaijser, K., Lindstern, J. *ibid.* 1960, i, 724.
10. Edwards, J. H., Harnden, D. G., Cameron, A. H., Crosse, V. M., Wolff, O. H. *ibid.* p. 787.
11. Patau, K., Smith, D. W., Therman, E., Inhorn, S. L., Wagner, H. P. ibid. p. 790.
12. Hayward, M. D., Bower, B. D. *ibid.* Oct. 15, 1960, p. 844.
13. De Carli, L., Nuzzo, F., Chiarelli, B., Poli, E. *ibid.* July 16, 1960, p. 130.
14. Sandberg, A. A., Crosswhite, L. H., Gordy, E. *J. Amer. med. Ass.* 1960, 174, 221.
15. Jacobs, P. A., Harnden, D. G., Court-Brown, W. M., Goldstein, J., Close, H. G., MacGregor, T. N., Maclean, N., Strong, J. A. *Lancet*, 1960, i, 1213.
16. Stewart, J. S. S., Sanderson, A. *ibid.* July 2, 1960, p. 21.
17. Fraser, J., Campbell, J., MacGillivray, R. C., Boyd, E., Lennox, B. *ibid.* Sept. 17, 1960, p. 626.
18. Jacobs, P. A., Harnden, D. G., Court-Brown, W. M., Baikie, A. G. *ibid.* Aug. 13, 1960, p. 368.
19. Ford, C. E., Jones, K. W., Miller, O. J., Mittwoch, U., Penrose, L. S., Ridler, M., Shapiro, A. *ibid.* 1959, i, 709.
20. Scandinavian cases cited by Fraccaro et al. (footnote 21).
21. Fraccaro, M., Kaijser, K., Lindsten, J. *Lancet*, Oct. 22, 1960, p. 899.
22. Böök, J. A., Santesson, B. *ibid.* 1960, i, 858.
23. Swanson, C. P. Cytology and Cytogenetics; p. 188. London, 1958.

pyridoxine, which alters tryptophane metabolism; or by administering saccharolactone, which inhibits enzyme activity in the urine; or by altering the urinary pH. Whether it will be possible by chemical means to prevent so-called "recurring" tumours, which may, in fact, be new tumours due to the persistence of a carcinogenic stimulus, depends on whether the mucosal changes are reversible or whether, once the mucosa has been stimulated by a chemical carcinogen, neoplasia is inevitable even if the stimulus is removed. Double-blind trials now in hand may provide the answer.

In the treatment of the established case one adverse factor that can be attacked is delay. Patients often recognise hæmaturia as a symptom of possibly grave significance. But this view is not always shared by the patient's doctor, who may treat painless hæmaturia, without associated frequency or pain, as a case of cystitis; and when the bleeding stops the patient and his relatives are lulled into a false sense of security. In hospital, too, the possible gravity of the cause of hæmaturia is often not appreciated: recently a patient with this symptom was given an appointment to be seen in the outpatient department three months later. We accept pain in the right iliac fossa as a matter of urgency. Why cannot hæmaturia be given similar priority? In cases of carcinoma of the bladder, when the delay between the onset of hæmaturia and treatment is less than a month the 3-year-survival rate is 70·5%; but when the delay is 6 months the 3-year-survival rate drops to 36·8%.[1] Quick and accurate diagnosis is possible, and this is likelier to improve the results than any changes in the techniques of radical surgery or radiotherapy.

In the past ten years surgery and radiotherapy have each held sway in turn. Nowadays the limitations of surgery and the dangers of excessive radiotherapy are appreciated; the surgeon and radiotherapist work as a team, seeing, treating, and following up each case together. This makes for better results—for example, in cases treated surgically in which metastases develop and require irradiation, and in cases treated by radiotherapy in which surgery is needed for resultant complications.

Many factors, including the age and general condition of the patient, must be taken into account in treating bladder tumours. When the disease is localised and confined to the mucosa the choice lies between intensive diathermy (either cystoscopic or open) or some form of radiation. The complications of intracavitary radiation—contracted bladder, mucosal atrophy, and hæmorrhage—have led to its abandonment in such cases until better techniques can be evolved. Diathermy—either electrocoagulation or electroresection—is therefore the method of choice. The skilled surgeon can deal with even large tumours by this method; but this technique cannot be safely left to a junior. For limited tumours infiltrating no farther than the muscle coat interstitial irradiation may be applied. Formerly such tumours would have been treated by radon seeds, but nowadays artificially produced radioactive isotopes (gold or tantalum) are used. This represents a technical improvement; for radioactive gold grains are smaller, safer, more accurately implanted, and obtainable in various strengths; while tantalum is relatively cheap, has a much longer half-life than gold, and can be kept at hand so that after cystoscopy the bladder can be opened, the tumour excised, and wire implanted at a single operation.[2]

The supervoltage radiotherapy beam, directed either from generators, such as a linear accelerator or a Van de Graaf machine, or from artificially produced isotope bombs (teleçobalt or telecæsium units), also has a place in treatment. This therapy can render a bladder tumour-free, but sometimes it completely fails to affect the tumour. Furthermore external radiotherapy in high dosage can produce radiation damage to the pelvic contents, including loops of small intestine. These risks, though small, must be weighed against the possibility of cure and the chance of conserving a normally functioning bladder. Using a linear accelerator at 8 MeV MORRISON[3] found that with a tumour dose totalling 4500–5500 rads in 4 weeks, 31% of patients had no tumour visible on follow-up cystoscopy. There was a better response with the earlier tumours (mucosal tumours disappeared completely in 43%, and a further 19% became appreciably smaller) but the more advanced tumours also regressed in many cases. These results show that supervoltage therapy is an extremely potent weapon and should be considered before recourse to radical surgery.

Partial cystectomy has tended to fall into disrepute, largely because it has been employed in the wrong type of case. MAGRI[4] has found that with single lesions, irrespective of the histological type (80% were solid anaplastic and infiltrating), where a clear margin of at least an inch was obtained there was a 71% 5-year-survival rate. Where, however, the line of excision cut through the tumour or its submucous extensions there were no survivors after 5 years. Partial cystectomy, though fairly easy, should be undertaken only after careful thought.

Radical surgery following radiotherapy is not difficult provided that irradiation has not been applied over too short a time to too large a volume of tissue or in excessive dosage. Radical cystectomy involves the removal of all the pelvic contents except the rectum, and also the lymph-nodes along the iliac vessels. WALLACE[5] has found that this operation, undertaken after radiotherapy, as the last weapon in the therapeutic armoury, carries a mortality of 21%; but that it can prolong life by 3 or more years in half the cases of mucosal tumours, a third of the cases in which muscle is infiltrated, and a quarter of the cases in which the perivesical fat has been invaded.

The treatment of bladder cancer is still far from satisfactory, but much can be done with our present

1. Report from the Institute of Urology and Southern Metropolitan Cancer Registry.

2. Bloom, H. J. G. *Brit. J. Radiol.* 1960, **33**, 471.
3. Morrison, R. *Clin. Radiol.* 1960, **11**, 125.
4. Magri, J. Personal communication.
5. Wallace, D. M. *Brit. J. Radiol.* 1960, **33**, 487.

resources to check the disease. It is heartening to know that a subcommittee of the International Union against Cancer has agreed on a provisional method of classifying and reporting cases, similar to that adopted for cancer of the breast.[6] If this recommendation is accepted the analysis of results should be greatly simplified.

Annotations

POMP AND CIRCUMSTANCE

THE ceremonial ward round has long been a familiar feature of our teaching hospitals. The Chief, surrounded by acolytes and disciples, proceeds in pomp from bed to bed, pausing now and then to correct a point of history, to confirm or deny the physical findings, to discuss the differential diagnosis, or to pontificate on methods of treatment. Ward-clerks and dressers stand around, shifting from foot to aching foot; bored registrars converse in whispers; nurses tiptoe past with bedpans; patients lie glum and silent while the Round drones on.

Is this the best way of teaching " bedside " medicine and surgery? The *Oxford Medical School Gazette* [7] thinks not. In a pungent editorial, entitled " Is Your W.R. Really Necessary? ", the *Gazette* reminds us that such methods are frequently discourteous and may sometimes harm patients. There the patient lies, sometimes half-naked, a forgotten object while the discussion rages over his bed. He is listening, moreover, with apprehension to the list of alarming investigations proposed for him, to talk of frightful-sounding diseases that he might have, sometimes to obvious differences of opinion about treatment. The more intelligent and educated he is, the worse his ordeal, for the more likely is he to glean from unguarded remarks some of the grimmer truths about his illness and to penetrate the thin veil of medical euphemisms. It is easy to forget that nowadays, thanks to television and other media of mass information, many patients have a smattering of medical terminology and jargon. And even if the Round removes itself a few beds away to discuss prognosis, other patients have ears, and ward gossip spreads. The physical suffering imposed on ward-clerks by the peripatetic ward round is a less serious matter; but they might listen better and learn more if allowed to sit down comfortably.

The *Oxford Medical School Gazette* suggests that all " bedside " teaching should take place in a room adjacent to the ward, with chairs, blackboard, and X-ray screen, into which patients can be brought when needed, or from which the Round can emerge for a brief visit to the bedside. This sensible idea has already been adopted by some teaching hospitals. We commend it to all. Such an arrangement has the additional advantage of ensuring that the formal " round " is recognised as purely for teaching purposes, as it should be, and is not mixed up with the day-to-day management of patients. It is impossible to teach properly on more than a few cases at a time. Practical therapy should be dealt with by the Chief later, when he goes round his beds privately with his junior staff. The traditional royal progress from bed to bed, with a gracious greeting and a few pearls of wisdom dropped at each one, may awe the impressionable but is not the best way either to teach clinical medicine or to cure patients.

6. See *Lancet*, 1959, ii, 958.
7. *Oxf. med. Sch. Gaz.* 1960, **12**, 41.

NEONATAL RESPIRATORY DISTRESS

RESPIRATORY distress in the premature infant is a common cause of neonatal death. Most of the affected infants have no evidence of congenital malformation or birth injury; hence they should survive if the distress could be prevented, and their recovery should be complete if it were more amenable to treatment. The challenge to obstetricians (for prevention of prematurity is the best means of preventing these deaths) and to pædiatricians is being met, and there is some encouraging progress to report.

In the past, research into respiratory distress has been largely concerned with the pulmonary and circulatory aspects.[1] This has proved less enlightening than was hoped; for the ætiology of pulmonary hyaline membrane remains obscure,[2] and the reported disturbances in the mechanics of breathing do not add greatly to our understanding, nor do they suggest any sound alternatives to present methods of treatment based on the administration of oxygen and nursing the infant in a humid atmosphere.

Interest has turned towards the biochemical changes associated with respiratory distress, and this may well prove a more productive approach. The present position has been well summarised by James.[3] Infants with birth asphyxia or respiratory distress become severely acidotic with hyperkalæmia, hypoglycæmia, and possibly hypocalcæmia. These changes are the expected consequence of anoxia and retention of carbon dioxide. They may well be responsible for death; and treatment with glucose, bicarbonate, and insulin holds out some promise of success.[4]

The maintenance of a stable blood hydrogen-ion concentration (pH) depends on the lungs and on the kidneys; and the newborn baby is unique in both pulmonary and renal function.[5] Some of the peculiarities of this period are now being elucidated. Helen Reardon and her colleagues [6] have reported the results of a technically brilliant investigation into the chemical aspects of the control of respiration in the early newborn period. They sampled blood not only from the umbilical vessels at birth but also from the temporal artery at various periods afterwards. They analysed the blood samples for plasma pH, CO_2 content, protein, O_2 content and capacity, and hæmatocrit. From these measurements the pCO_2, buffer base, and oxygen saturation were calculated. The results showed that the normal full-term infant is born with mild acidosis which is of both metabolic and respiratory origin. This is presumably due to an excess of fixed acids or deficiency of base which is uncompensated by hyperventilation. The rise in pCO_2 (respiratory acidosis) suggests that the birth process not only prevents compensation of the metabolic acidosis but leads to impaired CO_2 elimination. Within an hour of birth the respiratory component disappears owing to the efficacy of pulmonary ventilation, but the metabolic acidosis (decrease in bicarbonate or other buffer anions) tends to increase. There is thus a state of uncompensated metabolic acidosis. During the next few hours ventilation becomes efficient enough to compensate for the metabolic acidosis, and in some infants there is evidence of respiratory alkalosis. Correction of, rather than compensation for, the metabolic acidosis takes place in breast-

1. Cook, C. D., Barrie, H., Avery, M. E. *Advanc. Pediat.* 1960, **11**, 11.
2. See *Lancet*, Nov. 5, 1960, p. 1014.
3. James, L. S. *Pediatrics*, 1959, **24**, 1069.
4. Usher, R. *ibid.* p. 562.
5. See *Lancet*, 1960, i, 583.
6. Reardon, H. S., Baumann, M. L., Haddad, E. J. *J. Pediat.* 1960, **57**, 151.

fed infants from the 4th day but is delayed in premature infants. Reardon et al. argue that plasma-pH is the main stimulus to respiration because, during the phase of compensating metabolic acidosis, there is still increased respiratory drive in the presence of lowered pCO_2 and plasma-pH.

McCance and Widdowson [7] have shown that the kidney of the newborn infant secretes an acid urine at birth and in the first 48 hours of life; the acidity is due not to acid phosphates but to a predominance of ammonium salts and organic acids, and Zweymuller [8] has identified some of these as emanating from the citric-acid cycle. Probably, therefore, the newborn infant depends greatly on pulmonary function for the maintenance of acid-base balance; when this function fails the metabolic sequelæ may be catastrophic, and perhaps the biggest change is the hyperkalæmia. Whether this hyperkalæmia is due predominantly to renal retention of potassium and excretion of sodium or to the excessive liberation of potassium from within cells is uncertain. It seems reasonable, however, to attempt to prevent the extrusion of potassium from the cells by adequate oxygenation and administration of glucose.

PRISONS IN 1959

LAST year, as the annual report of the Commissioners of Prisons [9] relates, the numbers of prisoners grew yet again (though it fell in the autumn); and the numbers of prison staff increased in rather higher proportion, although many more are still needed. New legislation had a rather greater effect on the prison population than usual, with a drop of civil prisoners from 744 to 265 due to the Attachment of Earnings Order and an extra 63 prostitutes under the Street Offences Act. Imprisonments without fine continued to rise (by over 2500 to 28,411 for men) as did receptions of men not under sentence (by 1000 to 45,000). This means, as the commissioners say, that a regrettably large proportion of the effort of local prison staff is diverted from training persons convicted of crime. For women this defect is even more evident; for only 47% of those remanded before sentence were given imprisonment, and some 85% of these were imprisoned for not more than six months. There is a widespread feeling that some alternative must be found to short prison sentences, and the new Criminal Justice Bill published last week (its terms are summarised on p. 1082) may lead to their abolition at least for young offenders. The suspended sentence was buried in 1952, and the Advisory Council on the Treatment of Offenders in 1957 [10] did nothing to disinter it. The Council did, however, approve adult attendance centres and call for wide use of remand on bail for full inquiry between conviction and sentence, believing that the knowledge gained in this way would help magistrates to avoid giving imprisonment. Lord Kilmuir [11] offered detention centres as an alternative for under-21s—a group of prisoners which increased enormously in 1959 (by over 700 to 2498). Nevertheless, for men, sentences of under three months and over three years are tending to diminish slightly and intermediate ones to increase.

Regarding types of offence, convictions for violence against the person again increased, though this may only reflect changes in public attitude and sentencing policy: Gordon Hawkins [12] has described grounds for believing that in the past half-century violent crimes have not increased significantly. Sexual offences continued their downward trend, but not those against females. Thefts of all kinds again increased, but imprisonment for drunkenness decreased (by about 200 to 3129). Heavy traffic and current anxieties about road deaths were doubtless partly responsible for the great increase in imprisonment under the Highway Acts—at 2627 the total last year was nearly 50% greater than in 1958. The views of Lady Wootton [13] and others are evidently making some impact on her fellow magistrates. (Even so, the Royal Automobile Club [14] has pointed out that, while all traffic offences increased by 6·6% in the year, traffic volume went up by 10%.) Local prisons, unfortunately, still carry the greatest load, holding about 4 prisoners to every 1 accommodated elsewhere. Clearly "show" prisons such as Wakefield tell but a small part of the story.

Breaches of discipline and escapes continued to cause concern. Birching was ordered 11 times (3 in 1958), and this punishment was confirmed in 2 cases by the Home Secretary (0 in 1958). That 1 of these 2 men committed a second assault shortly afterwards must reinforce the belief that the value of corporal punishment is mainly to assuage the feelings of the staff. In the contrary direction, however, the approach towards a "therapeutic community" proceeds. The Norwich system of freer association between staff and prisoners continued to expand, and group counselling [15] spread to fourteen more prisons and borstals in the year. Even at Dartmoor, this system has had a good reception. Evening classes are expanding; but progress towards the realistic full-time work and reward system, so essential in training a man for ordinary life, is still disappointingly slow. Nevertheless, an Advisory Council on the Employment of Prisoners has been set up, together with a new post of assistant commissioner (industrial). It is one of the anachronisms of the age that thousands of able-bodied men moulder away in gaols while public works, such as waterways and the decaying relics of the 1939–45 war, lie neglected. But at least the pre-release hostel and training scheme is spreading as its success becomes more obvious. Another means of reintegrating the offender with society is by home leave; over 300 borstal lads were thus paroled, and only 1 in 30 broke it.

Detention centres remain one of the brighter hopes of the commissioners for coping with the "bulge" of moderately delinquent youth; and the new Bill seeks to make wider use of these centres. But, despite great shortage of places, unsuitable lads—persistent offenders, the physically or emotionally disturbed, and approved-school failures—are too often sent to these centres, where they are not helped by the brief period of highly disciplined and energetic life, and where their presence has an adverse effect on others. A better system of classification or of advice to magistrates is needed. Whether this stern type of institution is more effective than milder methods has still to be shown by valid comparative techniques. Over 50% of boys discharged in 1956 and 1957 had been reconvicted by 1960, and this does not sound too hopeful. Aftercare, as the commissioners sadly note, is not yet

7. McCance, R. A., Widdowson, E. M. *Acta pædiat., Stockh.* 1960, **49**, 409.
8. Zweymuller, E. *ibid.* p. 591.
9. Report of the Commissioners of Prisons for the Year 1959. Cmnd 1117. H.M. Stationery Office. Pp. 198. 9*s.* 6*d.*
10. Alternatives to ShortTerms of Imprisonment. H.M. Stationery Office, 1957.
11. *Times*, Aug. 9, 1960.
12. *Criminal Law Review*, October, 1960.
13. Wootton, B. Social Science and Social Pathology. London, 1959. See *Lancet*, 1960, i, 1238.
14. *Times*, Aug. 10, 1960.
15. See *Lancet*, 1959, ii, 1015.

compulsory; but the new Bill includes provisions for its extension to those coming out of detention centres.

Physical health in prisons remains good, and the trend towards using outside facilities continues; but the number found insane on remand jumped to almost double despite a decline in the number remanded for mental observation and report. It is hard to explain these trends; perhaps the new outlook inherent in the Mental Health Act of 1959 may have permeated the prison medical services more quickly than it has influenced the judicial authorities.

The prison services, avowedly therapeutic organisations these days, are under as much obligation as, say, the manufacturers of drugs to assess and to publish their results, particularly where new techniques such as group counselling are introduced. In a recent lecture the Home Secretary [16] endorsed the views on research we put forward last year.[15] It is therefore disappointing to find so little about new methods in the report. In support of group counselling it includes a few staff impressions and a couple of letters from prisoners; only in an appendix is there some worth-while evidence—from a local prison where, despite a rising population, the Norwich system led to a drop in disciplinary reports of 131 to 369, and the continuing lapses were less serious than before. Other than this, the cynic might be led to correlate the trend towards easier relationships in and out of the prison with the increase of indiscipline, escapes, and overcrowding which the report mentio... A larger chapter on "Research" is needed in this valuable document. The Home Office research unit, which is already doing a great deal, should stop hiding its light under a bushel. Bricks and mortar may still be badly needed, but knowledge must be given a new priority.

HUMORAL AGENT IN MIGRAINE?

BROADLY speaking, the mechanism by which symptoms are produced in an attack of migraine is agreed; but the exact changes in cranial blood-vessels and nearby structures which cause the characteristic head pains are still in dispute.

Chapman et al.[17] working on the hypothesis that besides local vascular change some inflammatory or pain-producing substance was produced locally, examined tissue-fluid from regions of the head which were tender during a migraine attack. Specimens were collected by slowly injecting 2 ml. of sterile physiological saline solution into the local subcutaneous tissue and then gently withdrawing some of it. Controls were provided by taking samples from the scalps of migraine patients both during attacks and at other times, from people not subject to headache attacks, and from the subcutaneous tissue of the forearms of each subject. In the headache subjects a substance was found which bioassay suggested was a polypeptide. This substance, for which Chapman et al. suggest the name "neurokinin", was present in small quantities in all specimens from all subjects; but very much larger quantities were found in tissue-fluid from the scalp of patients with headaches at the time the specimens were taken. It was also found to be released into the segmental cutaneous tissue-fluid during dorsal root stimulation and in the axon flare reaction. In one subject the substance was apparently reduced in amount after administration of ergotamine tartrate; and Chapman et al. suggest that interference by ergotamine with an enzyme system liberating "neurokinin" from a plasma-globulin may be the basis of this effect.

These results are extremely interesting. They may possibly explain some of the longer-lasting features of migraine which apparently outlast the aura and headache. But bioassay methods can be unreliable, and these findings will need to be confirmed and the substances if possible defined chemically.

TUBERCULOSIS IN AFRICA

IN the first of the four Heath Clark lectures, delivered in London on Nov. 2, Dr. Charles Wilcocks traced the development of investigations into tuberculosis in Africa. This disease, he said is still spreading; and drug treatment by itself is unlikely to provide the whole answer.

Wide variations in incidence and mortality among different races, noted as long ago as the beginning of the century, had led Cummins to formulate his "virgin soil" theory. According to this, primitive tribes were highly susceptible because, in the absence of the bacillus, they had never in their own surroundings been obliged to protect themselves against it; while those living in more urban communities had elaborated protective substances through contact with the bacillus. The high tuberculosis incidence and mortality among African troops in Europe in the 1914–18 war seemed to support this theory, though subsequent workers had suggested that the troops involved had been in France for some time and that they broke down under stress: in other words, that the cause lay more in the environment than in racial susceptibility.

Between the wars extensive work by individuals and commissions, ably supported by administrators, led to an accurate assessment of the distribution and character of the disease. It was found to be widely distributed and it progressed rapidly to death, with extensive cavitation and little fibrosis, and usually with involvement of both lungs. The sputum was heavily infected, and this was clearly a factor in spread when the patient and the rest of his family slept together in small, poorly ventilated houses.

Some idea of the distribution of the disease could be gained from the large proportion—41%—of the total health expenditure of the Union of South Africa devoted to tuberculosis. In the mines pneumoconiosis had added to the problem, although more careful selection of recruits and measures to cut down dust had reduced the number affected.

Treatment, previously limited to bed rest and an occasional pneumothorax, had been radically changed by the advent of effective drugs. But these might fail to control the disease, especially if the patient was not treated in hospital, because many did not take *p*-aminosalicylic acid with their isoniazid, and others stopped treatment before they should. Thus resistance developed on a large scale.

B.C.G. vaccination was sometimes the only rapidly applicable preventive measure; and its value was probably small. But these were short-time measures. For widespread improvement, the attitudes of members of very different cultures had to be modified and research undertaken into the means of persuading whole communities to change habits which favoured the development of tuberculosis. The most pressing need was improvement

16. Penal Reform and Research. By R. A. BUTLER. Liverpool: University Press. 1960. Pp. 14. 3*s*. 6*d*.
17. Chapman, L. F., Ramos, A. O., Goodell, H., Silverman, J., Wolff, H. G. *Arch. Neurol.* 1960, **3**, 223.

in environmental conditions. The emphasis had now shifted to stress as the main causal factor in tuberculosis. Nutrition, housing, working conditions, and hygiene and sanitation all required attention. The £10 million per annum spent by the South African Government in the past five years on housing for non-Europeans was a step in the right direction. It was unfortunate that the World Health Organisation, in its last report on the subject, had barely touched on the environmental factor, presumably because it was considered self-evident. But anything which was not mentioned tended to be forgotten.

It was the doctor's duty to stimulate the administrators to improve conditions, just as had been done in England a century ago.

A SEX-LINKED FAMILIAL PURPURA

THE classical sex-linked hereditary bleeding diseases are hæmophilia and its close relation, Christmas disease. In the past six years there have been reports of a purpuric hæmorrhagic disorder with a similar mode of inheritance by a sex-linked recessive gene—i.e., the condition affects males but is transmitted by female carriers who are unaffected, and each male has an equal chance of being affected or free. The condition, first described in 1954 by Aldrich et al.,[1] presents the odd combination of thrombocytopenic purpura, eczema, and undue liability to infection. In the family, of Dutch extraction, observed by Aldrich et al., the male infants were known to be liable to die in the first few years of life with "draining ears, eczematoid dermatitis, and bloody diarrhœa"; in the last three generations 16 out of 40 males had died with this disease before the age of 31 months. Krivit and Good [2] investigated the same family in 1959 and found that there were 2 female carriers who were reproducing, and that these had had 8 children since 1954; 2 were healthy girls and 6 were boys, of whom 3 had the disease and 3 were healthy.

2 cases in an English family have now been reported by Gordon,[3] of Sheffield. He points out that seven families affected by the disease have been described, one of them a Negro family. Details of 16 male patients are known, and all have died; 1 of Gordon's patients has died, and 1 is still alive.

Gordon's 1st patient was admitted to hospital at the age of 14 months with infantile eczema affecting the head, neck, arms, and legs. A bleeding tendency had been noted from the age of 4 months, and this had alarmed the mother because she had had a brother who had died of "hæmophilia" at the age of 1 year. Investigation showed severe thrombocytopenia, which persisted except for short periods when the count rose above 100,000 per c.mm. Bone-marrow was found to contain platelet-forming megakaryocytes. With treatment the eczema improved, and the patient was sent home. He was in hospital again on account of eczema five months later; and at the age of 4 years he was admitted with profuse purpura, bleeding gums, discharging ears, and impetigo. The thrombocytopenia being still present, it was decided to carry out splenectomy, and this was followed by a rise of platelets to normal and disappearance of the purpura. But in the next twelve months the patient had to be admitted three times—once because he had meningitis due to pneumococcal and staphylococcal infections, once for dental extraction which caused no trouble, and finally in a fatal coma. Necropsy showed bilateral adrenal hæmorrhages; there was no evidence of septicæmia; the platelet-count was not recorded.

1. Aldrich, R. A., Steinberg, A. G., Campbell, D. C. *Pediatrics*, 1954, **13**, 133.
2. Krivit, W., Good, R. A. *A.M.A. J. Dis. Child.* 1959, **97**, 137.
3. Gordon, R. R. *Arch. Dis. Childh.* 1960, **35**, 259.

Gordon's 2nd case was the brother of his 1st patient, born eight years later; in between, a healthy girl and a healthy boy had been born. This 4th child of the family showed eczema at the age of 3 months, and a month later he was investigated in hospital; he had thrombocytopenia, and furunculosis, pyuria, and bronchitis developed while he was in hospital. His white-blood-cell count was normal; and he did not have deficient γ-globulin. Treatment with prednisolone and then with corticotrophin produced only a temporary rise in the platelet-count. In view of the experience with the elder boy splenectomy was not performed, and the patient has remained reasonably well for three years, still having occasional purpura and occasional attacks of respiratory-tract infection.

This syndrome will be easily recognised, though we have no doubt that children with eczema and thrombocytopenic purpura will be seen who do not have the syndrome; the added features of recurrent infection and, above all, a positive family history must also be found. The cases so far reported have not been very fully investigated. Krivet and Good sought platelet agglutinins but did not find them; marrow punctures have shown the same picture as that of "idiopathic" thrombocytopenic purpura; γ-globulins appear normal. But nothing is known about the other blood-clotting factors. No attempt seems to have been made to find out whether the condition is linked in any way with systemic lupus erythematosus and similar diseases, in which thrombocytopenic purpura is sometimes an early sign. We hope that pædiatricians will look out for cases of Aldrich's syndrome and see whether more can be learnt about its ætiology and possible lines of treatment.

CHEMICAL MENINGITIS FOLLOWING SPINAL ANÆSTHESIA

FORMERLY, when measures were not taken to avoid contamination of the subarachnoid space with phenolic disinfectants, chemical meningitis was a recognised sequel of spinal anæsthesia.[1] Sterilisation by autoclaving of special packs containing all the equipment, including the ampoules of local anæsthetic, required for this form of anæsthesia is now commonly practised to prevent this complication. But autoclaving by itself is inadequate if the syringes and needles have not been previously freed from all traces of disinfectant by cleansing and washing.

The dangers of inadequate washing of equipment are well brought out in an account of five patients in whom acute meningitis developed very shortly after spinal anæsthesia for obstetric delivery.[2] The cerebrospinal fluid in each case was purulent, with a polymorph leucocytosis. These findings, together with pyrexia, suggested bacterial infection of the subarachnoid space, but no organisms could be isolated from the cerebrospinal fluid or from blood samples. A review of the procedures used for cleansing spinal anæsthetic equipment in the obstetric department concerned revealed that, whereas the ampoules of local anæsthetic were taken directly from their carton before autoclaving, the syringes used were soaked in a solution of a phenolic disinfectant, washed and rinsed, and finally put in trays ready for autoclaving. Clearly this washing was ineffective. Fortunately, all five patients recovered without permanent neurological sequelæ. Their illnesses illustrate once again the dangers associated with this mode of anæsthesia when insufficient precautions are taken to avoid contamination of the subarachnoid space.

1. Rendall, C. M. *Anæsthesia*, 1954, **9**, 281.
2. Goldman, W. W., Sanford, J. P. *Amer. J. Med.* 1960, **29**, 94.

Points of View

FUTURE ROLE OF THE FAMILY DOCTOR *

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WITH the changing patterns of disease in Western societies, particularly the emergence of the chronic diseases (heart-disease, cancer, peptic ulcer, bronchitis), of accidents (especially motor-vehicle accidents), and of the multiple effects of radiation as the characteristic and newly important threats to the public health, there has come the possibility of a rather different sort of medical care. This new approach is preventive in attitude (though the borderline between prevention and very early treatment is rapidly becoming meaningless). It is preventive in the sense of using our growing epidemiological knowledge accurately to define vulnerable groups, families, and individuals in our population and of manipulating their personal and social environment to prevent disease. But the differences between the present and future preventive medicine are more important than they seem at first sight. These days (and at long last) most of us accept the necessity for clean milk and the quality control of food, for example, without demur. These controls are, for the most part, satisfyingly impersonal. But just let us try advocating changes in the individual and family dietary customs of the healthy rather than the sick in our practices, or their leisure pursuits, or try to change one of many minor addictions to which we are all prone, and we are in for trouble. That trouble is made subtly worse by a sneaking feeling that we may have no right to meddle in these personal matters anyway, and that our techniques, if we do, are naïve. Yet, if the future general practitioner is to attempt the control of chronic disease in his practice, he has little choice—he *must* meddle, and his meddling must be increasingly personal, for it seems very likely that before long our so-called " new " diseases will offer as much of a threat to life and happiness as did some of the epidemics of the 19th century. And, since many of these diseases have their origins in our changing ways of living, a tolerable amount of interference may help to prevent them.

By " new " diseases I do not mean only novelties but *newly important* diseases which, because of their increasing contribution to our morbidity and mortality, must be counted as new threats. For example, with the decline (but not the defeat) of the infections we can see more clearly the enormity of our chronic-bronchitis problem (25 million man-days los per year, and thousands of deaths), of our cancer problem (100,000 deaths per year), of heart-disease, and of chronic but not always fatal diseases like diabetes and multiple sclerosis. We see, too, the useless (though fortunately small) waste of fœtal and neonatal life and the few remaining maternal deaths in a new context: the context of a society which, perhaps unlike all previous societies, does not expect illness and early death and which thinks of health and happiness as its right.

* * *

We can summarise the main features of our changing disease patterns in this way. First, the *vulnerable age-groups* are shifting. Young people are seldom ill. In fact the older children and adolescents have virtually disappeared from the doctor's surgery. There is increasing emphasis on the intrauterine child and the neonate, rather than the infant. Then there is the new interest, of course, in the elderly, and above all a growing anxiety about the middle-aged. The *sex ratios*, too, are changing, and the new diseases are increasingly selective of males.

Next, the *type of disease* is changing (and, inevitably, our attitude towards it). For example, infectious disease outbreaks are often spectacular and explosive; cases occur near one another; a hundred or so deaths in a small community has the impact of disaster, while the same number of deaths spread over the whole country—motor-vehicle or coronary deaths, for example—does not carry the same provocative danger signal. Some catastrophe is needed to promote social action.

Next there is the *duration of illness*. Most of our new diseases are chronic slow-moving processes which may take many symptomless years to develop. We are told that the cancer of the lung, for example, may have started fifteen or twenty comparatively healthy years before the first symptom of the disease, and that the men now dying of chronic bronchitis may well be reflecting not only their smoking habits and the air pollution of the cities in which they have lived but also the shorter convalescence enforced on working-class families by the tough economic pressures of the hungry '30s. It is, perhaps, this very long duration of our chronic diseases and of cancer which is doing most to force us to review our methods of medical care.

Finally, we can say that with a few exceptions our new threats to health seem, by their very nature, somewhat less likely to respond to curative medicine than the diseases of the past. However, this point is not a strong one, and, to strengthen the case for a review of our preventive measures, I would say that, thanks to the impeccable epidemiology of people like Doll, Case, and Morris, the prevention of many cancers (and some other chronic diseases) is becoming possible long before the disease itself is fully understood. Thus, in the face of our new diseases, *prevention* acquires a new urgency, and the wise family doctor is being forced increasingly to switch his attention from sick people to the habits and behaviour of healthy people many years before the clinical onset of illness.

* * *

So here, very crudely, is the problem. Most people who feel ill seek medical care and have a rather special relationship with their doctors. Healthy people, on the other hand, are unlikely to be particularly impressed by talk of a disease which *may* come in twenty years' time. Their replies to doctors who seek to change their behaviour, and thus to promote their future health, are polite but negative.

The dilemma is most acute for the family doctor, for it is now becoming technically possible for a large part of his job to be the highly scientific supervision of healthy people. Indeed, this looks like being the only way to cope with our new diseases. Such a statement does not sound particularly surprising, but at the moment well over 90% of the family doctor's work with adults is curative, dealing with established disease. If even a quarter of his work were to be concerned mainly with

* Abridged from a paper read to the sociological section of the British Association on Sept. 2, 1960. The full text will appear in *Advancement of Science*.

healthy people, rather than the sick, this would be a revolutionary change—at least as revolutionary as was his assumption of the role of vaccinator and immuniser of children. Such a change has been made *necessary* by the changes in our disease pattern, and *possible* by a growing knowledge of the reasons for variation in the vulnerability of different age, sex, and social groups. This means that the doctor who really knows how his patients live will be able to define with increasing accuracy who is likely to become ill. In fact, he alone—because of his contact with the family—can become the man to observe those aspects of behaviour which we suspect are the precursors of much chronic disease.

As a help toward the practical application of this change of approach, the doctor now has a growing armoury of screening devices and simple tests by which he can pick the already ill from among the merely vulnerable people in his practice, and so make earlier and ever earlier diagnoses. Many of these screening tests are sensitive enough to be used while the patient is still feeling fit—that is before he would normally seek medical care, and long before serious symptoms arise.

* * *

These notions may be illustrated briefly by reference to cancer of the uterine cervix. Epidemiologically speaking, this cancer is well described. A lot is known about what sort of people get it (but, of course, very little about how they get it). Through relatively simple technical advances it is becoming possible to make increasingly early diagnoses of the developing growth. We are told that treatment at an early stage is relatively easy and safe, but that the diagnosis must be made before the symptoms and signs develop. We are also told that the test is rapidly achieving real accuracy. So it is this combination of good epidemiology (which could guide the doctor to where the disease will arise—so that he need not screen all the women in his practice) and this early test which has suddenly given the family doctor the power if not to eradicate the disease then perhaps drastically to reduce it in his practice. But, at once we are back with the same problems as before. How to persuade apparently healthy women who belong to the vulnerable age, parity, and social group to seek medical care long before they feel ill; how to persuade the doctor to persuade them; and finally, how to fit this approach into a service and a society quite naturally preoccupied with curative medicine.

* * *

Tests which can be used for screening apparently healthy populations for all manner of different diseases are rapidly increasing in number and accuracy. They are an exciting product of the growing gadgetry of medicine. Already it seems probable that more or less accurate and very early diagnoses (that is, long before the patient is conscious of illness) can be made in a variety of chest conditions, a few cardiovascular disorders, some renal diseases, and an assortment of hereditary metabolic upsets, mild diabetes, and at least one cause of blindness.

In this way it seems that our new diseases are themselves forcing us into at least the contemplation of a different sort of medical care. This medical care may in turn need a rather different sort of doctor to apply it. Such a man would have different interests and would need much more time than today's family doctors whose hospital education very properly emphasises curative medicine above all else.

There are other difficulties apart from those of time and interest. For example, most doctors feel that, at least at first, we should play a passive waiting role: the initiative obviously should be with the patient. With this in mind most of us would find it very difficult, for example, to write to a lot of healthy adults on our lists inviting them to undergo even the simplest of screening tests. It would be even more difficult to go to the length of reorganising our practices so that much of our time was spent in this way.

There is yet another problem. How could the future family doctor screen the vulnerable people on his list, offer his genetic counsel, advise effectively on diet, exercise, and so on, or even check the blood-pressure and weight of the paunchily middle-aged (if one day it is agreed that these too are useful screening tests) without creating not a healthy practice but a practice of neurotics? We have seen a suggestion of this mass fear of illness following the indiscriminate "check-up" campaigns, the cancer films, and the commercial exploitation of anxiety which has occasionally been a feature of "health education" elsewhere. Our small experience of studies over here, and the wider experience of calmly and well run studies of community health (such as that at Framingham in the U.S.A.), suggest that these dangers can be avoided. But they remain an important threat; and the prevention of some heart-disease, for example, might save the lives of mentally healthy men at the cost of converting them into cardiac neurotics.

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Changes in disease patterns must always have given rise to new social problems: our current transition from the infections to chronic degenerative disease is obviously no exception. The changing role of the general practitioner is among the most intriguing of these problems, and it may be that in future he will have to be prepared to make himself more of a nuisance to his patients. But if he does, will they take any notice of him—and why should they anyway?

Public Health

Infectious Diseases in England and Wales

Disease	Week ended October				
	1	8	15	22	29*
Diphtheria	4	3	4	4	..
Dysentery	477	500	600	465	581
Encephalitis:					
Infective	1	3	4	2	3
Postinfectious	3	..	2	2	..
Food-poisoning	287	225	188	181	196
Measles, excluding rubella	3996	2856	3220	3917	4585
Meningococcal infection	19	28	29	19	18
Ophthalmia neonatorum	24	16	24	31	9
Paratyphoid fever	6	7	12	4	7
Pneumonia, primary or influenzal	175	202	239	213	221
Poliomyelitis:					
Paralytic	12	14	8	10	13
Non-paralytic	6	4	7	1	2
Puerperal pyrexia	153	194	201	188	171
Scarlet fever	305	357	424	465	409
Smallpox	..	..	..	..	..
Tuberculosis:					
Respiratory	387	386	428	436	343
Meninges and C.N.S.	2	2	2	2	6
Other	48	44	47	57	51
Typhoid fever	5	4	1	..	3
Whooping-cough	1110	1024	934	860	964

* Not including late returns.

Special Articles

EAST-WEST SYMPOSIUM ON PATHOGENESIS OF ESSENTIAL HYPERTENSION *

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"ALTHOUGH it appears that essential hypertension is a widespread condition and a frequent cause of premature invalidism and death, there is little agreement about its pathogenesis or about the role of various environmental factors in its production. This lack of knowledge prohibits any rational attempt at prevention. It seems desirable, therefore, to discuss the conflicting views and to delineate fields in which future research might possibly be concentrated with profit."

These were the broad terms of reference of a symposium which was held in Prague early in the summer under the joint auspices of the European Region of W.H.O. and the Czechoslovak Cardiological Society. Some 40 workers, engaged in research on various aspects of hypertension, attended, chiefly from the U.S.A., U.S.S.R., and Great Britain; but almost every other country in Europe was represented.

The detailed proceedings of the conference will be published shortly, and these will include an account of individual papers and the variety of opinions expressed in discussion. Nevertheless it seems worth while to record some personal impressions now which it is hoped may give some idea of the positive achievements of the symposium. Research on hypertension has recently received a fresh stimulus from several different directions, and this was reflected in the lively controversy and some new ideas which found expression during the symposium.

One stimulus in Prague was undoubtedly the opportunity of hearing from Russian investigators about their concept of essential hypertension as a specific neurosis, against the experimental background of hypertension induced in animals by nervous or emotional strain. New interest has also been aroused by epidemiological studies on the role of genetic and environmental factors, one outcome of which is the current controversy on whether essential hypertension is a disease entity or a biological variation differing only quantitatively from the normal. Furthermore, the widespread use of hypotensive drugs with a variety of pharmacological effects has not only emphasised the need for a clearer understanding of the fundamental nature of the disorder, but has also produced some new ideas about possible mechanisms in its pathogenesis. In the investigation of these problems, statisticians, physiologists, experimental pathologists, and pharmacologists are becoming increasingly active. The old controversies about humoral and neurogenic mechanisms have been given a new look by the discovery of intriguing relationships between renin and aldosterone, by more critical assessment of the role of catechol amines, and by the researches of neurophysiologists in several countries on the nervous regulation of the circulation. Added to this is a questioning of the old concepts of the hæmodynamic status in hypertension in which circulatory changes were accepted as incidental to a primary increase in peripheral resistance, so that the search for ætiological factors was focused almost exclusively on this restricted part of the vascular system.

The symposium was arranged as a series of discussions on the following topics: definition, diagnosis, and natural history; epidemiology; the role of emotional and environmental factors; neurogenic factors in the control of blood-pressure; hæmodynamic studies in essential hypertension; vessel-wall factors; metabolic factors, including the possible role of pressor amines, the adrenal cortex, and the kidney.

Although there was considerable divergence of opinion on most of the topics discussed, there was a fair amount of agreement on the nature of the problems which need to be tackled. These I have attempted to summarise in the following questions:

(1) In the light of modern knowledge, can we arrive at any more satisfactory definition of essential hypertension than the present one of "elevation of the blood-pressure without apparent cause"?

(2) In view of the more exact methods of diagnosis now available, how large a proportion of cases, masquerading under the diagnosis of essential hypertension, are really due to some local disease—e.g., of the kidneys or endocrine glands?

(3) Is it possible to find a means of separating normal from high blood-pressure, not only in the numerical sense, but also in establishing whether essential hypertension is qualitatively different from the physiological range of the blood-pressure?

(4) How valid are casual blood-pressure readings, especially when used as an index in epidemiological studies? How far can such blood-pressure readings be standardised?

(5) How large a part does heredity play in the pathogenesis of essential hypertension? Is the genetic factor sufficiently large to indicate a primary metabolic fault in blood-pressure regulation as the main cause?

(6) What is the role of environmental factors such as geographical situation, diet (including electrolyte intake), occupation, and particularly, mental strain or emotional stress?

(7) Does the blood-pressure rise with age uniformly in the population as a whole, or is there an excessive rise in a limited group, who as they get older emerge from the normal population owing to the development of a specific disease, essential hypertension?

(8) How often does "transient" or "intermittent" hypertension lead to established hypertension—i.e., is there a definite sequence in the natural history from transient to permanent elevation of the blood-pressure?

(9) Can a prehypertensive state be recognised in which metabolic or vascular responses may make it possible to anticipate the development of essential hypertension?

(10) What part do nervous, renal, and endocrine mechanisms play in determining peripheral vascular resistance? Is there any real evidence that these factors play a different role at different stages of the disease?

(11) Is the regional distribution of increased peripheral resistance the same in all cases? Is it different in the early and late stages, and does it differ from the distribution in other hypertensive disorders such as renal hypertension?

(12) Is it possible that, with advancing age, some alteration in the vessel wall may produce a change in reactivity to physiological stimuli?

For the various topics in the symposium, discussion leaders were appointed, and produced a day-to-day progress report. In the final discussion on "topics and future trends for research arising from previous dis-

* This article is based on a summary review of the symposium presented to the Czechoslovak Cardiological Society, and a lecture on experimental hypertension to the Czechoslovak Nephrological Society, Prague, June, 1960.

cussions " an attempt was made to coordinate the results of the conference, particularly with a view to international co-operation in various fields. In what follows, I have tried to give a brief account of the general conclusions on the various topics seriatim, but it must be recognised that on some issues there is still considerable disagreement on both the validity and the interpretation of the available evidence, or on its relevance to essential hypertension.

Definition and Natural History

On the question of *definition* it was generally agreed that at present there is no satisfactory alternative to the term essential hypertension, indicating " a common form of high blood-pressure without apparent cause ". Whilst modern diagnostic techniques are revealing increasing numbers of cases due to specific lesions, such as renal-artery stenosis, pyelonephritis, or endocrine disease, this is almost certainly a minority group—not large enough, for example, to invalidate epidemiological studies based on measurements of blood-pressure as the sole criterion. In the individual it is impracticable to define a critical dividing-line between normal blood-pressure and essential hypertension; but this is equally true of other forms of hypertension—e.g., that due to renal disease. Whether essential hypertension is a disease entity, qualitatively different from the physiological range of blood-pressure, may well be decided by a critical analysis of existing epidemiological data, together with further planned investigation of selected populations. If indeed we are dealing with a specific disease, some biochemical fault should eventually be discovered. There is evidence that patients with essential hypertension do show qualitative differences from the normal—for example, rapid electrolyte diuresis following plasma-volume expansion by a water or solute load, reversal of the normal antidiuretic effect of injected angiotensin, and the recent evidence of increased secretion of aldosterone in malignant hypertension—but it has yet to be shown that these differences in behaviour are specific for essential hypertension and that they are primary rather than secondary manifestations.

One of the most urgent needs is a clearer definition of the *natural history* of the disorder. Physiologists, experimental pathologists, and epidemiologists are tending to interpret their various data in terms of the " early " or " late " stages of the disease, but there is as yet no clear understanding of these stages or indeed of the relationship of transient to established hypertension. It may well be that further clarification of the natural history will emerge from characterisation of the various states (if these exist) by biochemical or physiological tests. Thus, response to salt-loading or angiotensin, or differences in secretion, utilisation, or end-organ response of adrenal cortical hormones, may be found to differ in different clinical groups; or again there may be a change in hæmodynamic pattern in terms of cardiac output and distribution of regional resistance. Possibly nervous and humoral factors play different roles in the early and later stages. We know, for example, that a minority of cases, especially in young subjects, have an increased cardiac output. Whether this is due to anxiety at the time of the investigation and whether it can still be demonstrated after hypertension has persisted for many years needs to be determined. Whilst some of these questions—e.g., a better definition of stages of the disease—may be answered by large population studies, most of them will require long-term and more detailed investigation of small numbers of patients by the clinician and experimentalist working together. For, apart from problems of differential diagnosis, it will be essential to recognise the intrusion of secondary factors, such as local atherosclerosis, altered renal function, or emotional reactions, which may modify the physiological pattern and bring into play new homœostatic mechanisms.

Epidemiology

The starting-point of epidemiological studies is the validity of blood-pressure estimation as an index. Examination of the " casual " blood-pressure should be made to see whether further standardisation of technique is possible and what additional criteria can reasonably be included in population studies. The epidemiologist is on uncertain ground until the validity of the high casual pressure as an indication of essential hypertension is assured. But if this can be established, some of the really fundamental problems of ætiology may be solved by epidemiological methods. The most important of these is *heredity*. If the genetic factor in essential hypertension is of major importance there is an urgent need to seek for an inborn error of metabolism in the pathogenesis of the disease. Even if there is a specific genetic factor, the environmental situation may well determine whether this defect leads to manifest disease. Furthermore a distinction (commonly overlooked) must be made between genetic factors and the " cultural inheritance " which is also transmitted in the family. The influence of *age* is the second main problem which epidemiological studies should be able to resolve, for if a substantial rise in blood-pressure can be shown to develop in a discrete section of the population as age advances, in contrast to little or no rise in the remainder, there can be little doubt that essential hypertension exists as a separate entity; furthermore the search for a causal mechanism can then be directed to changes in function with advancing age. There is a good deal of evidence, at present difficult to evaluate, of blood-pressure differences between population groups, which may be related to ways of life. It is in the epidemiological field that international cooperation is likely to be most fruitful, particularly in the investigation of racial factors, the effects of diet, the stresses of industrialisation, and other circumstances where differences in prevalence, already recognised, present " experiments of opportunity ".

The Neurogenic Hypothesis

The view that essential hypertension has a neurogenic basis is undoubtedly enjoying a new wave of popularity. Investigators in the Soviet Union have for some years maintained that essential hypertension develops as a specific manifestation of neurosis, and this has led to observations on the prevalence of hypertension in different occupation groups, to extensive physiological researches on the nervous regulation of the circulation, and to studies in dogs and monkeys of experimental hypertension produced by stress stimuli using conditioned reflexes and Pavlovian techniques. The widespread use of hypotensive drugs which act centrally or peripherally by inhibiting autonomic vasoconstriction has produced in some quarters an uncritical acceptance of the neurogenic theory, or at any rate of an important nervous component in essential hypertension. Supporting evidence has been sought, particularly in the United States, by analysing the

emotional and hæmodynamic responses of hypertensive individuals to stressful situations, or by studying cultural background, character structure, and behavioural patterns in relation to the incidence of the disease. Owing to lack of translations of published data it is impossible to give a fair assessment of the Russian view, and it is to be hoped that the clinical, experimental, and epidemiological evidence on which this concept is based will soon be made more readily available. At present most workers agree that in the established phase of essential hypertension—i.e., when the diastolic pressure is persistently raised—there is no convincing evidence that the cause is neurogenic vasoconstriction. That emotional stress can cause acute elevation in blood-pressure is undoubtedly true, but the relevance of this to the chronic disorder we term essential hypertension is quite obscure; and in neither transient nor established hypertension has increased autonomic activity been demonstrated by the finding of increased catechol-amine production, as is observed in patients with high blood-pressure due to phæochromocytoma. There is obviously a need for a more critical and broadly based assessment of hypertension of supposedly nervous ætiology in terms of its clinical characteristics, hereditary origins, and subsequent course. Furthermore when studying emotional responses in both personal behaviour and vascular reactivity, it is essential to establish to what extent these are the cause or the result of the elevated blood-pressure.

Hæmodynamic Changes

From what has been said it will be obvious that the largest single obstacle to understanding the genesis of hypertension is an imperfect knowledge of the factors which control the blood-pressure in health. It would be easier to decide whether hypertension was " abnormal " if we understood better the mechanisms by which normal blood-pressure is maintained. This becomes even more obvious when considering the further problems of hæmodynamic changes, vessel-wall factors, and the possible role of renal and endocrine dysfunction in essential hypertension. In the field of blood-pressure regulation, physiologists seem to have been until recently almost exclusively concerned with the autonomic control of vascular tone. In various discussions a great deal was heard about the baroceptors and other vascular receptor mechanisms, about cardiovascular changes following hypothalamic stimulation, and about the central and peripheral effects of hypotensive drugs on autonomic status and catechol-amine production. It is well established that the response threshold of the baroceptors is raised in chronic hypertension, but this appears to be an adaptation to the high blood-pressure rather than its cause. Recent physiological and pharmacological work has certainly revealed new aspects of neurogenic control of the circulation; but those who are concerned with the problem of hypertension, either clinically or experimentally, are questioning the adequacy of this approach, and are seeking information on other possible regulating mechanisms which may be more relevant in maintaining blood-pressure at a high level. For example, what controls the residual arteriolar tone when all sympathetic influences are removed? Is it some endocrine factor, a renal pressor substance such as angiotensin, or is it a question of the electrolyte environment of the smooth-muscle cells of the arteriole? Whatever the controlling factors, vessel tone varies under the influence of a number of stimuli, and this brings up the vexed question of vascular reactivity. Pressor responses to vasomotor stimuli such as cold, emotion, and vasoconstrictor drugs have so far failed to provide a convincing separation of hypertensive from normotensive subjects or to predict the future development of high blood-pressure in the latter. Yet the level of the blood-pressure alone is insufficient to explain individual differences in the production of both functional and structural vascular reactions—e.g., hypertensive headache, papillœdema, fibrinoid arteriolar necrosis and localised cerebral vasoconstriction in hypertensive encephalopathy.

In general the view has long been accepted that narrowing of the arterioles is the primary hæmodynamic change in essential hypertension. An alternative view is that vasoconstriction may occur as a reaction to increased intra-arterial pressure, which might be caused, for example, by a rise in cardiac output. This possibility has directed attention to primary changes in cardiac dynamics and to possible alterations in venous tone or venous blood-volume, which might affect cardiac output and thereby initiate arterial hypertension. Deviations from normal behaviour, such as the rapid salt diuresis in chronic hypertension, and the link between reduction in plasma-volume and blood-pressure after administration of diuretics such as chlorothiazide, have suggested a disturbance in the relationship between vascular capacity and blood-volume in the hypertensive patient. Various new and interesting techniques are being developed in an attempt to explore these possibilities. Methods have been devised for a more exact physical analysis of the parameters of vascular tone, and it is hoped that these may provide a means of identifying and assessing the effects of neurogenic and humoral factors, and of vascular " reactivity ", in hypertension of various sorts. Hæmodynamic studies on cardiac output, and on the regional distribution of peripheral resistance, suggest that in hypertension certain areas of the vascular bed—e.g., the kidneys and skeletal muscle—respond differently in different circumstances. Experimental models are also being devised in animals in an attempt to separate the cardiac component from the role of the peripheral circulation during changes in blood-pressure induced by various means.

Metabolic Factors

The symposium included a number of papers and a very critical discussion on the role of pressor amines, the adrenal cortex, and renal factors in the pathogenesis of essential hypertension. Most workers agreed that at present there is no direct or convincing evidence that either the kidney or the endocrine system plays a part in the early or later stages, although this may not be true in the malignant phase of the disease. Here again we are faced with the problem of distinguishing primary factors from secondary changes which develop in severe hypertension as a result of renal vascular damage. Such damage may produce metabolic disturbances—for example, in sodium and water excretion—and may possibly alter the pattern of hormone production (e.g., hyperaldosteronism in malignant hypertension). Nevertheless recent work on the reciprocal action of renin and aldosterone, and on the relationship of renin production by the juxtaglomerular apparatus to renal perfusion pressure, have produced, if not yet a promise, at any rate a hope, of a clearer understanding of renal participation in blood-pressure regulation.

There is another line of approach, based on both clinical

and experimental observations, which is certainly relevant to the problem of chronic hypertension in general, and possibly by analogy to essential hypertension. This is the growing evidence of a change in mechanism when high blood-pressure passes from the acute to the chronic stage. Thus when hypertension is caused by some specific lesion—e.g., phæochromocytoma, adrenal cortical tumour. or unilateral renal disease—the pressure frequently remains elevated when the primary cause is removed. As far as present evidence goes, it does not seem possible to distinguish this chronic residual hypertension from essential hypertension on clinical, physiological, or anatomical grounds. There is some evidence also of a difference in mechanism between the hypertension of acute and chronic nephritis and early and late experimental renal hypertension. These observations underline the importance, first, of looking for a similar change in mechanism in the development of essential hypertension, and, second, of considering the possibility of a common factor in the various forms of chronic high blood-pressure. The striking thing is that in all these conditions a new equilibrium appears to have been established at a high level of blood-pressure which is consistent with many years of good health. This would appear to involve a "resetting" of the homœostatic mechanisms which normally maintain arterial pressure at a steady level. There is evidence of such a resetting in the case of the baroceptors; but, as already mentioned, the evidence does not suggest that this is of causal significance. One of the most clear-cut observations in this field is the reversibility of chronic renal hypertension. In the laboratory animal, renal hypertension of long duration is reversed within a matter of hours if the renal circulation is restored to normal. In man a similar prompt reversal of chronic renal hypertension has been demonstrated when, in identical twins, a normal kidney has been grafted in a twin with chronic nephritis and the diseased kidneys removed. Thus it is clearly established that, in the maintenance of chronic renal hypertension, no irreversible extrarenal mechanism—structural or neurogenic—supervenes. This does not of course exclude the participation of some extrarenal factor, but it does indicate that in this form of chronic hypertension a metabolic renal disturbance almost certainly plays a primary role in resetting the homœostatic regulation of the blood-pressure at a higher level. In other forms of chronic hypertension, including essential hypertension, this line of reasoning is effectively blocked by the fact that, at any rate until the late stages, there is no structural basis for a renal mechanism. If therefore the kidney plays a role in the pathogenesis of essential hypertension it must be on the basis of a purely functional disorder, or of structural changes which have not been so far revealed by light microscopy. This is a main problem for future investigation. One of the most urgent needs is a further clarification of the mechanism of renal hypertension, for, from what has been said, this may open the way to an understanding of other forms of chronic high blood-pressure.

Views on the pathogenesis of essential hypertension have recently been expressed, on this and other occasions, in which the high blood-pressure is deemed to depend on a variety of influences—genetic, nervous, emotional, dietary, renal, and endocrine—with the corollary that no specific cause is likely to be found in the great majority of cases. These "multiple choice" hypotheses, which embrace all the possible mechanisms of blood-pressure variation, fail to distinguish, and indeed seem to discount the need to distinguish, these mechanisms from their provoking causes. The modes of production of blood-pressure elevation are undoubtedly manifold and may differ in the wide variety of individuals who present with arterial hypertension. But some single factor or limited combination of specific factors may well determine that one person gets "essential hypertension" whilst another does not.

Conclusion

From these far-ranging discussions I have attempted to outline recent trends in various lines of research which seem to offer promise for the future. The Prague symposium made a valuable contribution by bringing together workers from East and West, and by providing the fullest opportunities for critical discussion of their diverse views. It brought to the fore the problems and possibilities of epidemiological research on the subject, and presented fresh evidence and ideas on hæmodynamic factors. Perhaps of greatest importance was the large representation from the basic sciences—chemistry, physics, physiology, and pharmacology—for from these disciplines are most likely to come new techniques and methods of inquiry.

The programme arrangements of the symposium placed the emphasis on discussion rather than presentation of papers, and this was something of an experiment on which both W.H.O. and the Czechoslovak Cardiological Society are to be congratulated. What cannot be omitted is a sincere appreciation of the work and friendliness of our medical colleagues in Prague, whose hospitality was not only generous but very largely personal and spontaneous.

THE FUTURE OF GENERAL PRACTICE

THE future of general practice was considered by Dr. OSCAR WILLIAMS in a presidential address to the Association of Welsh Executive Councils at Llandudno on Oct. 28.

Dr. Williams remarked that it had been said that the general practitioner was dead. It was certainly true that, except in residential suburbs and south-coast resorts, applications for practice vacancies had fallen almost catastrophically. What was to be done?

The clock could not be put back: no practitioner could now, as he did formerly, cope with all emergencies and problems. But the pendulum had swung too far the other way, for today the practitioner was forced to refer a high proportion of his patients to a specialist or a succession of specialists before initiating treatment; and sometimes he might lose all control over his patient's treatment.

Inevitably the status of the practitioner (he could now hardly be called family doctor) had suffered—and this at a time when in the higher administrative places opinion was moving away from increased institutional treatment, particularly of mental illness, of the very young and very old, and even for midwifery.

Those who served on executive councils should welcome this rethinking, and should determine forthwith to play a more creative part in building a complete domiciliary service—an aim which could be achieved only in cooperation with the public-health, hospital, and social services. The general practitioner could then become more of a personal doctor, concerned with the social aspects of disease, able and willing to advise the family on its problems, the children, the aged dependants, and the difficulties when the family had to cope with a mentally ill member.

Unfortunately there was at present little incentive to this end. The Royal Commission on the Remuneration of

Doctors and Dentists had not supplied the answers: its report implied that indifferent work paid. The essential minimum requirements were as follows:

The practitioner should have more time to devote to each patient; and this entailed at once cutting big lists and lowering maxima.

He should be properly housed, with all the ancillary help he needed.

He should work closely with his hospital and other colleagues; and he should in fact be invited to participate actively in the work of the hospital and of local-authority clinics, thus averting the frustrations of overlapping.

He should be allowed far more practical participation in the work of hospitals. Clinical assistantships limited to six months' tenure were not the answer; nor even was the provision wherever possible of general-practitioner beds. A family doctor should be able to graduate into the hospital service, as he could formerly.

Another difficulty, which had been only half faced, was the general practitioner's security, or lack of it. The doctor should have the right, without fear of losing his patient, of advising the patient firmly on the course he should pursue, and not merely prescribe the latest tablet. A change of doctors should not be allowed without adequate grounds. Finally, there should be some recognition of higher standards of work.

PENSION AND BENEFIT INCREASES

THE proposed increases in pensions, benefits, and contributions, foreshadowed in the Queen's speech, were announced by Mr. John Boyd-Carpenter, Minister of Pensions and National Insurance, on Nov. 2. The increases, which will cost an extra £160 million a year, will, subject to parliamentary approval, begin next April.

War Pensions

The basic rate of pension for 100% war disablement will be raised by 12*s.* 6*d.* a week to 97*s.* 6*d.* Pensions for war widows with children, or over forty years of age, will be increased by 10*s.* a week to 76*s.*, with further increases for their children.

National Insurance Benefits

The standard rates of retirement and widows' pensions and sickness and unemployment benefits will go up to 57*s.* 6*d.* a week for single people and to 92*s.* 6*d.* a week for married couples, increases of 7*s.* 6*d.* and 12*s.* 6*d.* respectively. The allowance for each dependent child will be increased by 2*s.* 6*d.* a week, and for a widow's child by 5*s.* Maternity benefits, the guardian's allowance, and the child's special allowance are also being raised.

Industrial Injuries Benefits

Injury benefit, now 85*s.* a week, will be increased to 97*s.* 6*d.* a week, as will the pension for 100% disablement. The industrial widow's pension of 56*s.* a week will go up to 64*s.*

Contributions

The flat-rate contributions for employees in the graduated scheme will stay at about their present level instead of being reduced from next April. The flat-rate contributions for employees contracted out of the graduated scheme, for the self-employed, and for the non-employed will be increased. The contribution from the taxpayer will also be increased.

National Assistance

The scale rates for National Assistance will be raised by 3*s.* 6*d.* a week for a single householder and by 5*s.* for a married couple, to 53*s.* 6*d.* and 90*s.* respectively. There will be suitable increases in the other rates, including those for dependants.

Symposium

IMMUNOLOGY IN THE RHEUMATIC DISEASES

THE Empire Rheumatism Council held a symposium on Immunology in the Rheumatic Diseases in London on Oct. 28, under the joint chairmanship of Dr. W. S. C. COPEMAN and Prof. JOHN SQUIRE.

Dr. L. E. GLYNN (Taplow) said that immune tolerance was an acquired faculty, but one which could also be lost. He outlined possible ways in which antigen- or antibody-forming cells might be altered with subsequent breakdown or avoidance of tolerance mechanisms.

Dr. A. G. S. HILL (Stoke Mandeville) reviewed the clinical evidence that rheumatoid arthritis was a disordered immune response, and found little to indicate a hypersensitivity response.

Reporting a joint study with Dr. I. M. ROITT, Dr. W. HIJMANS (Leiden), and Dr. E. J. HOLBOROW, Dr. DEBORAH DONIACH (London) described results of testing sera from patients with thyroiditis, systemic lupus erythematosus (S.L.E.), and rheumatoid arthritis for the presence of antibodies to thyroid antigens, antinuclear factors, anticytoplasmic factors, and rheumatoid factors. About 10% of Hashimoto patients gave positive antinuclear or anticytoplasmic tests, and the incidence of low-titre anti-thyroglobulin antibodies was increased in S.L.E. patients.

Serum complement was diminished in S.L.E., Dr. H. A. ELLIS (Birmingham) found, and might be increased in early active rheumatoid disease, although it fell later, especially when rheumatoid-factor titres were high.

Dr. R. R. A. COOMBS (Cambridge) described the factor—immunoconglutinin—which appears in the serum of rabbits immunised with bacteria specifically agglutinated with antibody in the presence of complement, or indeed immunised with bacteria alone. This factor, apparently an auto-antibody to complement, can be detected in the serum in many human infections, but is increased also in rheumatoid arthritis.

Dr. R. G. WHITE (London) described the use of immunofluorescent methods to locate γ-globulin intracellularly in the plasma-cell series in the medullary tissue of lymph-nodes, and in their germinal centres. He drew attention to the follicular hyperplasia and plasma-cell proliferation found in rheumatoid lymph-nodes.

The significance of the rheumatoid serum factors was discussed by Dr. J. BALL (Manchester), who said that the rheumatoid macroglobulin factor for rabbit globulin could be detected in about 40% of adults, and in significant titre in 2–5% of Northern Europeans. Positive tests were found (apart from rheumatoid arthritis) in a significant proportion of cases of S.L.E., systemic sclerosis, digital arteritis, and Sjogren's syndrome. About 35% of positive tests in a random sample were associated with clinically detectable disease.

Dr. C. L. GREENBURY (Stoke Mandeville) described quantitative experiments using radio-iodine to label rheumatoid factor or antibody, which indicated that the amount of factor removable by repeated absorption from a given serum varied according to the degree of sensitisation of the absorbing red cells.

Dr. B. CRUIKSHANK (Glasgow) doubted whether γ-globulin was significant in the ætiology of rheumatoid disease. Only a minority of the plasma-cells in the inflammatory lesions of rheumatoid tissue had been shown to contain either 7S or 19S γ-globulin. He had found histological changes in synovial tissue in ankylosing spondylitis essentially similar to those in rheumatoid arthritis, but associated neither with serum

rheumatoid factor nor with increased serum-γ-globulin. In agammaglobulinæmic rheumatoid disease, too, plasma-cells were virtually absent from the inflammatory lesions.

Dr. J. N. McCORMICK (Stoke Mandeville) had used partially denatured human γ-globulin labelled with fluorescein to detect rheumatoid factor in unfixed frozen biopsy material from rheumatoid arthritis. The cells containing the factor were mainly plasma-cells, and were most numerous in rheumatoid synovial tissue. The globulin of the germinal centres, although abundant, appeared to contain very little rheumatoid factor.

Fluorescence methods of locating tissue antigens (using fluorescein and rhodamine conjugates) were also described by Dr. G. SCOTT (Stoke Mandeville). Using anti-glomerulus and antisynovial-membrane conjugates, he had defined three components of human connective tissue by immunohistochemical staining.

Dr. W. R. M. ALEXANDER (Edinburgh) had found that synovial fluid from rheumatoid-arthritis patients injected intradermally in other patients or controls, often gave rise to a delayed skin reaction, apparently of the Mantoux type. The active factor, a γ-globulin, was very unstable, and usually did not cause a reaction in the donor's own skin.

Discussing his experience with antinuclear serum factor as revealed by the fluorescent-antibody method, Dr. D. M. WEIR (Taplow) said that the factor was almost invariably present in S.L.E., but was also found in rheumatoid arthritis, discoid lupus, and some other related conditions, although much less frequently and usually in lower titre. He described laboratory investigations on the nature of the antigen(s) reacting with the serum factor.

Dr. G. J. FRIOU (Yale) had studied antinuclear factor using fluorescent and radioactive labelled antihuman globulin with whole nuclei, and nucleoprotein, as antigens.

Dr. W. HIJMANS (Leiden) regarded the L.E. cell factor as an antibody against nuclear material, and described quantitative precipitin studies between desoxyribosenucleic acid and serum, and complement-fixation studies with histone. He gave reasons for not considering the serum factor as pathogenic.

Dr. E. J. HOLBOROW (Taplow) considered the antigenic possibilities of the polysaccharides of connective tissue. He outlined natural and experimental methods of enhancing antigenicity of polysaccharides and drew attention to the lack of knowledge of whether they could take part in hypersensitivity reactions.

Medicine and the Law

The New Criminal Justice Bill

THIS Bill deals mainly with offenders under 21. Its main objects are to make wider provision for the use of borstal training and of detention centres in dealing with young offenders; to discontinue short sentences of imprisonment as more detention centres become available; and to extend the provision of compulsory aftercare. Changes are also proposed in the law relating to approved schools.

Part I remodels the custodial forms of treatment for young offenders. No new forms of treatment are proposed, but existing methods, particularly borstal training and detention centres, are extended to more offenders. Imprisonment will eventually be restricted to cases where no other sentence is appropriate. The new scheme depends on the provision of more borstals and more detention centres, and will be introduced by stages as the additional institutions are ready.

Borstal Training

The minimum age for a sentence of borstal training is lowered from 16 to 15 and the court will be able to pass such a sentence whenever they think it expedient that the offender should be detained for training for not less than six months. But if an offender is under 17, the court, before passing a borstal sentence, must decide that no other method of dealing with him is appropriate. The maximum term of borstal training is reduced from three years to two years and the minimum term from nine months to six months.

Imprisonment

The imprisonment of young offenders is restricted to sentences of not more than six months or long sentences of three years or more (except for some offenders who have already been in prison or a borstal). Short sentences of imprisonment are to be abolished by stages as more detention centres become available. Imprisonment of offenders under 17 is abolished, but the power of the higher courts to sentence children and young persons found guilty of grave crimes to detention as the Secretary of State may direct is extended. At present, this power is confined to offences of attempted murder, manslaughter, or wounding with intent to do grievous bodily harm. The Bill extends it to include any offence for which an adult could receive a sentence of 14 years' imprisonment or more.

Detention Centres

Where the court decides that a short period of training is appropriate, the offender will be committed to a detention centre. For offenders until 17 dealt with by a magistrates' court, the period of detention will be a standard term of three months. The higher courts will have discretion to fix the period of detention within a minimum of three months and a maximum of six.

Approved Schools

The law about committal to an approved school is not altered, but the Bill provides that a boy or girl of not less than 15 can be removed temporarily from an approved school on a justice's warrant, if this is necessary to maintain discipline, to another approved school, a remand centre, or a remand home for up to twenty-eight days. Offenders who turn out to be unsuitable for approved-school training, but are likely to benefit from borstal training may, with the consent of the Secretary of State, be brought before a magistrates' court, which will have power to order their transfer to borstal.

Attendance Centres

The minimum age at which a child may be ordered to attend at an attendance centre is reduced from 12 years to 10.

Fines

New and, in general, higher limits are set to the fines that magistrates' courts may impose in respect of offences committed by children and young persons, and the obligation on a parent to pay damages of costs awarded against his child is extended to the payment of compensation for loss. Enforcement of fines will be by committal to a detention centre or a remand home for offenders under 17.

Compulsory Aftercare

This is usually undertaken by probation officers. It is extended for the first time to all offenders who are released from a detention centre (unless they were sent there for a default) and to some categories of people released from prison. The extension of compulsory aftercare to ex-prisoners will be introduced by stages. When it is completed it will include all sentences of four years or more whatever the age of the offender; all sentences of six months or more where the offender was under 26 at the start of the sentence; and all sentences of six months or more when the person has previously had a prison sentence of three months or more or a borstal sentence.

In England Now

A Running Commentary by Peripatetic Correspondents

ONCE again the Director-General's Exercise—this year named White Swan—gave us a programme packed with interest, a shop-window of ideas for the future. Some will be discarded, but others will bear fruit. I asked three very senior officers what was the biggest problem facing the Army Medical Services today. One said the acquisition of broader professional experience. Another said the recruitment of other ranks (and gave me an entertaining lecturette on how to do it). The third said transport, transport, and transport again. If you can transport the sick and wounded, quickly and shocklessly, over long distances to the medical centres, you can economise in medical manpower and equipment—and that appeals both to the operational commander, who wants to slim his administrative tail, and to the manpower planner, faced with a return to voluntary service after twenty years of conscription. Transport today and tomorrow means air transport (the day after tomorrow it may mean hovercraft or rockets) and the D.G. duly showed us long-range aircraft, the rotodyne, helicopters—the lot. A French general told us about the enormous use made of helicopters by the French army in Algeria. The six-year-old Algerian war has given the French more experience than any other nation of air evacuation, but he indicated that the French Army did not want to go on accumulating this experience.

We also saw the latest types of civil ambulance cars, some with bodies completely constructed of plastic reinforced with glass-fibre, which is strong, light, rustless, and never needs painting. Yet with road congestion getting worse every day, will not the local health authorities have to invest in helicopters? Let the R.A.M.C. show the way. At the Cambridge Hospital they could establish an accident centre, equipped with helicopters and aerial cameras, to serve the whole of the Aldershot district. The casualty department would be staffed with surgeons of the requisite experience, a helicopter-ambulance could be at the scene of an accident in a matter of minutes (even on bank holidays), and every accident could be photographed from the air. What a contribution such a unit could make to research into the causation, prevention, and treatment of road accidents!

An excellent curry—made with dehydrated ingredients and served in a hangar—revived our spirits after the cold of the airfield. We saw the impressive efforts which are being made to modernise and improve military medical equipment. The Plastic Age is dawning, and the reductions in total weight and bulk are nothing short of dramatic. The new lightweight medical panniers were demonstrated by an extremely smart Nigerian private who has won the Duke of Edinburgh's gold award.

I am not yet convinced of the value of the universal container—a lightweight room that can be carried by air and deposited on any little flat piece of ground. We saw it being used as an operating-theatre, as a pathology laboratory, as an advanced medical store, as a heatstroke centre, and as the examination and treatment room for a 10-bed medical reception station. Perhaps it was the sight of ten "patients" lying in bed in the pouring rain (were there not enough canvas roofs to go round?) that made me feel that further experiment in the design of tentage and supports is what is really needed. The School of Health gave us an admirably straightforward demonstration of ten basic health routines for the soldier, after which there was a bit of a barney about urine tests for paludrine.

The Exercise gets more like an international congress every year. None of the American officers would hazard a guess on the result of the Presidential election. Eminent officers from the Indian subcontinent spoke to me gloomily about the changed status of their 2000-year-old Maginot Line of the Himalayas. A Canadian officer told me that the integration of the Canadian Forces medical branches (which so bewitched our political mentors in the Select Committee on Estimates) had scarcely changed anything. Just at present, integration seems to be more urgently needed in certain political circles than anywhere else. At the Exercise supper a well-known authority on malaria prevention presided with patriarchal dignity over a table of pretty nursing officers, and somebody round the piano sang "I'm Dreaming of a White Swansong".

* * *

I am, I confess, a secret thinker, and one day in the rush-hour I caught myself at it again. Suppose a Neptunian scientist (people on Neptune are very large) knowing nothing about life on Earth were to hover over some of our greater cities, studying the traffic. He would notice that the multi-coloured shining particles which moved in certain natural channels appeared to obey certain laws. These laws, it is true, would not always be rigidly followed; they would be approximate, statistical, stochastic laws, similar to those of chemical kinetics and thermodynamics in our own scientific culture. He would observe, for example, that when a space appeared among a stream of particles, one of them would inevitably sooner or later move into the gap, so that the place left behind it could in turn be filled by another particle and so on, giving the overall effect of a sluggish wave-like forward motion. He might well postulate some kind of force, tending to move the particles by mutual pressure into regions of low population density. "Nature", he might aphoristically say to himself, "abhors a vacuum." Or he might notice that when the population-density was high, the noise-level also tended to be high; or there might be a relation between the average rate of the forward wave-motion and the density, or between the noise-level and the mean distance travelled without collision. In short, our Neptunian might soon build up a set of traffic laws akin to the gas laws of physics.

At this point in my meditations I stopped my forward wave-motion with something of a jolt, causing a transient sharp rise in the local noise-level. If a Neptunian were to look on us like that, would he be doing anything fundamentally different from what we do when we study the molecules of a gas? And would it ever occur to him that each one of those curious shiny particles, with their semi-random, semi-determinate motions, might contain a living, sentient, meditative being such as myself? Well, then, how about the gas molecules? Who might there not be inside them, I asked myself. And, do you know, the thought has bothered me since. After all, how do we know that an atom doesn't think of itself as ME? It's time somebody looked into the matter, in my opinion, because if we go on treating the atoms the way we do now, some day there'll be trouble.

* * *

We had a rotten trip back fom the States. Even the official log of the *Mauretania* described the conditions as "strong N'ly gale, very rough sea, very heavy N'ly swell". After long deferment of hope in successive arrivals at Cobh and Le Havre, we reached Southampton. I telephoned my wife and arranged for her to meet me in Newcastle at 7 A.M. The boat train took me to London, where I boarded the sleeper at King's Cross.

I woke up at 6 A.M., and reflected that this was the ninth day since leaving New York, but that I would be home in an hour. The attendant brought tea. I remarked that it seemed very quiet outside. "Yes, Sir," he said, "I'm afraid we're still in Northallerton, and we're an hour behind time. I'm just going to find out what's the matter." He was back in a few minutes to say: "It seems, Sir, that the fire went out. They're busy trying to get it going again."

Not even the rich new expletives that I had learnt in America were of any use to me: I was speechless.

* * *

Our quiet, shy, third-year medical student disappeared behind the screens to examine a middle-aged blonde patient. All was well for a few minutes as his examination proceeded, but suddenly the quiet of the ward was shattered by scream upon scream and the words: "I wouldn't even let my husband do that." The student emerged blushing furiously to explain to

Sister, who advanced in a menacing way, that he had only been eliciting the patient's plantar responses.

* * *

A long time ago I made the mistake of learning how to use a desk calculating machine. It was useful to me at the time, because I do not like doing sums and it was much nicer to have a thing like a typewriter to do them for me. But it got me a reputation which did me no good at all, and I became known as the department's statistician (unpaid and quite extra to my proper jobs) and general calculator-man. I have never been strongminded enough either to repudiate the status or to insist on people learning to do sums for themselves. Now, to put the seal on my position, I have been sent on a computer course because " it might be useful if you get the know-how ".

I must say the computer people were very nice and friendly to us. (I could be friendly too, if someone wanted to learn from me how to use my little desk machine instead of wanting it done for him.) Their machine was friendly too; a bit dour the first time we called on him, but then he was said to have a pain in his inside, and an appreciable smell of beer in his neighbourhood suggested that he knew how to look after himself when out of sorts. Later he was in splendid form, inverting a large matrix and playing a happy tune on his hooter to announce progress after each thousandth sum or so—i.e., a brisk toodleoodleoo, with a thousand to each " ooo ". Our job, it appeared, was to learn a language which he could understand well enough to translate into his own dialect; and presently we were writing

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A = 2
B = 2
A = AB
PRINT (A)
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which seemed a funny way of putting 2 × 2 and downright wrong algebra. But presently we grasped bits of it, and were happily composing letters to the supermachine and even typing them ourselves on the teleprinter which makes the only kind of signs he is really interested in reading.

By the end of the course the real mathematicians had become obvious, while some amateurs had fallen by the wayside altogether. This was not quite my fate, but I did get a bit mixed up about what was computer-work and what was not. I wandered into the unit's common room and was interested to find *The Times* with the crossword only half done. The supermachine couldn't have been too slow to finish; it was nice to think that in some ways he might have been too stupid. But then computers are apt to have a streak of stupidity: look at me still doing the department's sums for them. I never thought that this course would show me that what I have most in common with supermachines is a willing nature.

* * *

Aunt Pash must be one of my oldest patients. She is said to be 93, has one eye, and a colostomy. She lost her eye in " one of they girlish pranks ". I am not sure what she means by that, but knowing Aunt Pash, I fear the worst. I usually visit her hut on the beach when I am in that part of the district, but three times lately it has been empty, and neighbours told me that Pash was visiting. However, the last time I was up the Bay, she was home again, and her hut was, as ever, chaotic with spinning and quilting. This time there were no tales of her girlhood—the more lurid of which always ended with " Ah, my dear, the tales I could tell'ee, the tales I could tell'ee ". No, she had been out gallivanting, and mightily she had enjoyed herself. A distant cousin had moved house, and she had gone to help. Now it may not be remarkable for an elderly lady to hold very small pieces of china at a housemoving, but in Newfoundland housemoving literally means house-moving. The house is taken from its foundation, hauled down to the edge of the water, floated on to a raft, and towed to its new site. Once there it is dragged out and hauled into position. It is a backbreaking job, and all hands are needed on the lines. This is what Aunt Pash had been doing on her holiday. Later I was told that she had worked as hard as anyone and cussed better than most. I don't doubt it at all.

Letters to the Editor

FUTURE ORGANISATION OF PATHOLOGISTS

SIR,—Since with the approach of voting-day for pathologists, past-presidents of the Association of Clinical Pathologists have written to press the advantages of the recent " offer " of the Royal College of Physicians, I write to point to one important fact and event in the history of the Association that has been omitted from recent discussion and documents.

The Association of Clinical Pathologists became incorporated on Feb. 12, 1956. This was the culmination of the labours of a devoted secretary and had been pursued with enthusiasm by presidents, officers, and council, and the members and all knew that this was the initial stage in the formation of a new and independent college.

What is it, therefore, that has caused presidents, officers, and council now so eagerly to favour " the present generous and unequivocal terms " of the recent offer of the Royal College of Physicians?

That a diploma of membership of a division or faculty of a Royal college would be an almost immediate result of acceptance of the offer is certain, and this would meet one of the needs of pathologists without any great effort—merely the subscription of foundation membership, or examination and membership fees. But the status that this diploma might confer would be somewhat reduced by the inferiority attaching to a division or faculty. (That a faculty is regarded as inferior is witnessed by the current action of a most ancient medical faculty that seeks by legislation to alter its title to Royal College of Physicians and Surgeons of Glasgow.) Surely, the seniors in the Association are not unaware of this implication of inferiority which is not disguised by the use of the term division. Why is it therefore that they advise a " short-cut " when the Association has progressed to incorporation unaided? Everyone knows that a new and independent college may require a few years to have its diploma of membership recognised, everyone knows that a new college is not founded and nurtured without great effort and equally great sacrifice. Those who earnestly and sincerely consider that an independent college should be the heritage of our registrars, and in turn their registrars, would work willingly and make sacrifices. Is it that in the remaining years of their working lifetime the seniors would rather they held high office and examinership in a subsidiary faculty (of which they are fellows through being fellows of the parent college) than be concerned with great efforts the fruits of which would be enjoyed by posterity and not by themselves? Or, to put it at a higher level, is it that the senior pathologists who are fellows of the Royal College of Physicians are using their influence to secure to this college, at the time of rebuilding, and for a long time, revenue from the pathologists that in the first instance might amount to around £25,000?

London, N.18. J. F. HEGGIE.

SIR,—Dr. Joan Taylor and Professor Pulvertaft are two of my oldest friends, but I am bound to tell them that most of their letter of Nov. 5 is rubbish.

Professor Pulvertaft has had much experience in the appointment of pathologists. Has he ever found the absence of a specific higher qualification a handicap? And if so, how often? (In this debate a few quantitative statements will be refreshing.) He makes appointments, as

everyone else does, on the confidential advice of his colleagues and on his own judgment. If he has made an occasional mistake I have little doubt that it has been when the flutterings of his warm heart have silenced the warnings of his cool head. In our lifetime it has been characteristic of pathology—more, I think, than of any other branch of medicine—that it has drawn its adepts from a wide variety of sources: the preclinical sciences, public health, and general practice have all contributed colleagues whom we respect. There have been those pathologists who combined the humblest medical qualifications with fellowship of the Royal Society. It is one of the weaknesses of the N.H.S. that it is more difficult than it was to change from one specialised branch to another. To add any degree or diploma which makes the entry into pathology more difficult or more rigid can only impoverish the science.

"Academic centre" is, I suppose, looking-glass language for a college or faculty. The adjective is an unusual one to apply to any existing body of this kind except, perhaps, the Royal College of Surgeons. As for "a body to speak for pathologists", things have come to a pretty pass if Dr. Taylor and Professor Pulvertaft are no longer able to speak for themselves. To whom is this body to speak and about what? And who on earth would be able to speak for such a disorderly mob of individualists as we are?

In all this interminable debate the talk has always been of examinations and diplomas but seldom of training. Is it not time that we abandoned this babu attitude? The Doctor and the Professor and I all learned pathology in the bad old way, picking up knowledge and experience as we could, piecemeal and without a plan. The example of the course for the diploma in bacteriology has shown that a more systematic training is not only possible but desirable. I see no reason why the same methods should not be applied to other branches of pathology if some university will give them a trial.

Hoccombe, Somerset. J. A. BOYCOTT.

SIR,—For Dr. Joan Taylor and Professor Pulvertaft I have the greatest admiration and respect, but their idea of an academic centre for pathology in London seems completely out of touch with the ideas of those of us who work some distance from London.

The higher qualification and the body to speak for pathologists can be achieved at a very small cost. Dr. O'Gorman (Nov. 5) is rightly daunted by the cost of a building, but what pathologist outside London is going to use such a building?

For meetings, the Pathological Society and the Association of Clinical Pathologists have been able to enjoy the hospitality of numerous bodies all over the country. The College of Pathologists could do likewise.

Why should not the College of Pathologists start in a small way like the Royal College of Obstetricians and Gynæcologists?

As for withdrawing, as Dr. O'Gorman suggests, once we are in the Royal College of Physicians it will be impossible to withdraw from that body without its permission. The constitution of that body is authoritarian, and it would be unreasonable to expect permission to withdraw to be granted, as G. G. implies (Nov. 5, p. 1025).

No, Sir! The only solution appears to be the logical conclusion of Peter Davey's argument. He says that the physicians are notable Greek scholars. They therefore know that a pathologist is a man who studies disease. Their work is therefore pathology, not physic, which is the study of Nature.

Let them show their greatness by changing their name to the Royal College of Pathologists. We will then join in with them, so possibly will the other Royal Colleges! (Or am I optimistic?) We shall then have a body able to speak for the whole of Medicine.

The alternative more likely to be acceptable is for the pathologists to have their own College, and for all the medical colleges, faculties, associations, and societies to join together to form an Academy of Medicine for that purpose.

Mumbles, Swansea. H. C. M. WALTON.

SIR,—As an ordinary pathologist of a very peripheral hospital, may I support the plea of Dr. Joan Taylor and Professor Pulvertaft for a vote in favour of the division of pathology within the Royal College of Physicians. I started this year firmly in favour of an independent college and, because of the accident that it was my turn to be branch president, found myself defending this view on behalf of the North of England branch at a special meeting of the council of the Association of Clinical Pathologists held in February. Because of this I subsequently had quite a long exchange of views with various members of the council, and have since become convinced that a division within the Royal College of Physicians will meet our needs.

In the Widdicombe File, G. G. discusses the various obstacles in the way of an independent college and shows how they might be overcome, but he does not mention the greatest obstacle of all. This is that the great majority of the leaders of our specialty do not favour the establishment of an independent college at the present time, but, in all sincerity, prefer the R.C.P. solution. It seems to me that it is possible and right for the main body politic of the Association of Clinical Pathologists to stop—if it so wishes—its leaders from going a certain way; but more than this is not possible. The real issue in the forthcoming poll therefore is not between the R.C.P. and an independent college but between the R.C.P. and nothing at all for many years to come. With the Royal Commission finished, the next ten years may be all-important in shaping the future pattern of British medicine, and it will be bad for both medicine and ourselves if during this time we alone among the major specialties have no official organisation.

Northallerton. P. N. COLEMAN.

SIR,—Discussions on the future of clinical pathology have assumed that it has a future in the form we know today. The supporters of a College of Clinical Pathologists ought to discuss this assumption and have not done so; association with the Royal College of Physicians involves considerably less mortgage of the future.

We are not endowed with the gift of prophecy. Twenty-five years ago few would have envisaged the position that clinical pathology enjoys today. To assume that the present pattern will exist unchanged in 1985 is to make an improbable assumption. Two branches (hæmatology and chemical pathology) are growing rapidly and show signs of passing out of the ken both of the general physician and of the clinical pathologist. Hæmatology is already well on the way to becoming a subspecialty of internal medicine. More slowly, chemical pathology is going the same way; the advent of automation, lessening as it must preoccupation with technique, will accentuate this trend. Of the other branches of clinical pathology, hospital bacteriology is being divided more and more between the

specialists in hygiene and therapeutics. Remains pathology proper, the practitioners of which have always had a well-defined subject which does not take them to the bedside nor make them primarily technicians; it is probably the branch of pathology destined to change the least. It seems at least unlikely that most of the subject-matters of clinical pathology will remain in the hands of a group called clinical pathologists and a College of Clinical Pathologists, if established, could become another South Sea House and an obstacle to progress.

For reasons set out by Dr. Joan Taylor and Professor Pulvertaft present action is needed: such action should leave the future uncommitted as far as possible. Association with the Royal College of Physicians is the only logical course.

Sheffield. ARTHUR JORDAN.

*** A letter from the Widdicombe File appears on p. 1094.—ED. L.

USE OF BRL.1241

SIR,—Dr. Novick's letter (Oct. 29) covers well-trodden ground and adds little except speculation to what we already know. By now several thousand strains of *Staphylococcus pyogenes* have been tested, and so far no "celbeninase"-producing organisms have been found. This suggests that they are rare if they exist at all, and are considerably rarer than penicillinase-producers were at the time of the introduction of penicillin. On the other hand we are all agreed that bacteria often yield mutants which bypass the injurious effects of a chemical agent in some way other than destroying the drug. This is an alternative and more common method of developing resistance to an antibiotic. In the case of penicillin such mutants can readily be obtained by selection in the laboratory, but have not been shown to be the cause of lesions in man. Thus of the two kinds of resistance to penicillin only the one based on the destruction of the drug by an enzyme is clinically important. Since 'Celbenin' is a derivative of penicillin having in all probability essentially the same mode of action it would be reasonable to expect that resistant mutants (non-"celbeninase") might also lack pathogenicity, even though retaining coagulase and other characters. However, whether this expectation is unfounded, and strains *do* exist which retain sufficient virulence to be of clinical importance and in addition are endowed with sufficient communicability to occupy the biological space in hospitals, can be determined only by carefully controlled clinical observations.

The demonstration of celbenin-resistant staphylococcal mutants was probable on general grounds and would be expected to follow the pattern of multiple steps of mutation seen with penicillin, each step resulting in greater resistance. As the serum levels obtainable with celbenin at present are more restricted than with penicillin, it is conceivable that first or second step mutants could acquire sufficient resistance in vivo to escape therapeutic action, and yet retain pathogenicity. With spraying, however, this is less likely to occur since much higher concentrations can be achieved locally and the mutants succumb to the higher doses of the drug. Resistant mutants are not man-made, only selected, and on speculative ground at any rate are more likely to result from therapeutic use than from spraying.

Dr. Novick says that "... it is conceivable that the method might be used indefinitely without unfortunate consequences, and it could be argued that the risk involved is acceptable in view of the advantages. This risk must, however, be assessed in the light of the history of the fight against the staphylococcus ..." We submit that this is precisely what we did—bearing in mind the fundamental clinical problem of penicillin resistance.

It must be admitted that a complete victory along these lines is perhaps not in sight, but that should not make one jettison a line of research on theoretical grounds. The spraying of carbolic by Lister did not altogether banish hospital gangrene, but while it was in use undoubtedly saved a great number of lives. We believe that the discovery of celbenin by the Beecham group was a milestone in the history of antimicrobial agents and will certainly lead to new and powerful drugs in the future. In the meantime experiments with spraying should continue until their value is proved or their risk demonstrated on a factual basis.

Bacteriology Department,
St. George's Hospital
Medical School,
London, S.W.1. S. D. ELEK
P. C. FLEMING.

PROGNOSIS AND ANTICOAGULANT PROPHYLAXIS AFTER CORONARY OCCLUSION

SIR,—In their very valuable article of Nov. 5 Professor McMichael and Dr. Parry suggest that the unusually good 5-year survival-rate of doctors after cardiac infarction is because "no doubt they can take greater care of themselves and avoid undue physical strain". It is surprising that the authors, who are so rightly critical of loose thinking and imprecision in others, should make such a dubious statement. What does "taking care of themselves" mean? And what evidence is there that "avoiding undue physical strain" prevents further infarcts?

I submit that a more plausible explanation of the apparent good prognosis in doctors is that their minor cardiac infarcts are more often diagnosed than are the minor infarcts of the laity, the symptoms of which are apt to be attributed to "indigestion".

Farnham, Surrey. JOHN W. TODD.

POSTPARTUM PRE-ECLAMPSIA

SIR,—I have read Flight-Lieutenant McFadyen's article of Nov. 5 and should like to make the following comments.

I have already shown [1-4] that the contracting postpartum uterus provokes renal ischæmia (which incidentally ergometrine might heighten, and this is evident in all the cases reported); that renal ischæmia is responsible for hypertension, œdema, and albuminuria; that hydramnios is an agent provocateur of renal ischæmia (main case); that pre-eclampsia is to be suspected with even miminal signs of the syndrome (main case); that there are many conditions that post partum can masquerade as pre-eclampsia (case 2 certainly being one in point). In fact his case-histories, if interpreted in the light of the data I have provided, amply support the thesis that the uterus resisting tension, which it does post partum also, provokes the uterorenal reflex from which the signs of toxæmia can all stem.

Further I have collected sufficient evidence [5 6] to show that the symptomatology of toxæmia is not comparable to Cushing's syndrome; that as toxæmia mounts so do the corticoids decline; that corticotrophin (A.C.T.H.) when given experimentally in human pregnancy does not provoke the syndrome; that eclampsia does occur when the adrenals have been previously extirpated; and that the placental production of corticoids is very small in contrast to that of the adrenals.

May I also draw attention to two very important data?

1. Sophian J. Toxæmia of Pregnancy. London, 1953.
2. Sophian, J. *Excerpta Med.* 1958, sec. x, 2, no. 1.
3. Sophian, J. *Lancet*, 1960, i, 1351.
4. Sophian, J. *Amer. J. Obstet. Gynec.* 1959, 78, 688.
5. Sophian, J. *Lancet*, 1958, i, 434.
6. Sophian, J. *Amer. J. Obstet. Gynec.* 1954, 68, 733.

Garrod [7] found that there was an immediate increase in glomerular filtration-rate (G.F.R.) provoked by cortisone experimentally, while there is incontrovertible evidence to show that G.F.R. is much decreased in toxæmia.[1]

It would profit obstetricians to study the renal problem deeply. To this end may I congratulate you on your enterprise in publishing an account (Sept. 17) of the 1st International Congress of Nephrology at Evian, excellently compiled by Professor de Wardener.

Worthing, Sussex. JOHN SOPHIAN.

CHEMOTHERAPY IN CHRONIC BRONCHITIS

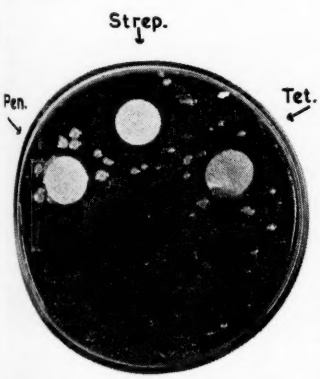
SIR,—The paper by Dr. Pridie and his colleagues (Oct. 1) and the letter by Dr. Aspin and Dr. Howells (Oct. 15) regarding long-term treatment of chronic bronchitis with antibiotics contain findings somewhat at variance with our own. The minimum recommended dose of tetracycline or oxytetracycline for the continuous treatment of chronic bronchitis is 0·5 g. daily, but we found 1 g. per day to be the minimum satisfactory dose. A smaller dose is in our view unlikely to be effective in the treatment of the majority of established cases of chronic bronchitis. It does not seem to be a fair test of the efficacy of therapy to use a smaller and relatively ineffective dose. With a dose of 1 g. daily we have shown that the side-effects are much less significant to the patients than the incapacity which results from acute exacerbations of the disease in untreated cases.

Further, the fullest bacteriological information can be obtained only by examining serial specimens of sputum freshly obtained from the patient. We have shown that the correlation of the findings obtained from a single isolated specimen of sputum with the clinical state of the patients is poor. The mere isolation of organisms not normally found in the respiratory tract, notably the coliform group, had little or no association with the clinical state of the patients, none of whom was treated in hospital.

Departments of Infectious Diseases and Bacteriology, City Hospital, Edinburgh. J. McC. MURDOCH J. C. GOULD.

SIR,—I note the letter by Dr. Aspin and Dr. Howells with particular interest because I have recently been associated with a clinical trial in chronic bronchitis to assess the value of vaccine therapy in contrast to the normal procedures of chemotherapy and antibiotic treatment.

During this trial samples of sputum from some 50 patients were examined and we were particularly struck by the suppression of the normal flora with stimulation of growth of coliforms in vitro, using antibiotic-disc technique (see fig.)



Stimulation of growth of *Klebsiella pneumoniæ* by antibiotics in sputum-culture from case of chronic bronchitis.

This has led us to believe, as your correspondents suggest, that in treating chronic bronchitis intermittently with antibiotics the suppression of the usual flora may lead to consequent increased growth of the coliform organism.

We have therefore persisted in our researches to determine what help vaccine therapy could give.

We have been using a polyvalent oral vaccine for this purpose, and have had a great deal of assistance from general-practitioner colleagues in this project. Should any of your readers be interested in helping us undertake a larger scale trial we should be grateful to hear from them and supply them with the necessary vaccine.

Woodlands, Windlesham, Surrey. R. E. DEREK LEIGH.

SURGICAL REMOVAL OF BRANCHIAL SINUS

SIR,—I should like to congratulate Mr. Allan Small on his article of Oct. 22. Whether the condition is fistula or sinus is still a debatable point, but at The Hospital for Sick Children, Great Ormond Street, there have been many true fistulæ.

This has been proved by the injection of dye into the track and its detection in the pharynx even before operation.

The only point in the article that causes some concern is that related to thyroglossal cysts and their tracks. I presume that Mr. Small implies that the more difficult part of the dissection includes the excision of part of the hyoid bone and the very careful removal of the proximal part of the track as far as the foramen cæcum.

If this point is not strongly stressed I am sure that the recurrence-rate in this condition will increase and lead to many more difficult secondary operations.

The Hospital for Sick Children, London, W.C.1. S. J. COHEN.

SIGNIFICANCE AND CLASSIFICATION OF FAT-EMBOLISM

SIR,—In his important paper of Oct. 15 Dr. Sevitt concludes that pulmonary fat-embolism produces no significant ill-effects in previously healthy subjects, and that it does not cause death even in those suffering from shock or blood-loss. The validity or otherwise of this conclusion is of great practical importance, for it must influence the rationale of treatment. If pulmonary fat-embolism is harmless then the thing to be avoided at all cost is systemic spread of the emboli, for there is general agreement that systemic fat-embolism is potentially a very serious condition. Acting on this belief, some German workers [1–3] have practised a prophylactic regime whose object is the maintenance of " controlled hypotension ", in order to reduce the risk of pulmonary fat-emboli being forced through into the systemic circulation.

I am less certain than Dr. Sevitt that pulmonary fat-embolism is innocuous when very severe or when associated with shock or hæmorrhage. The absence of a *characteristic* clinical symptom-complex does not necessarily mean that the condition is free from clinical manifestations of any sort. It must be conceded that intravenous injection of fat in animals may produce severe effects and even death; although the lethal dose may be considered high there is a considerable species difference in tolerance—the dog, for example, is much more tolerant than the rabbit [4 5]—and results should not be applied uncritically to man. Furthermore, there is abundant evidence that processes such as bleeding or the induction of tourniquet shock much reduce the tolerance of animals to intravenously injected fat.[4–8] The contrary finding of Armin and Grant [9] stands alone and

7. Garrod, O., Davies, S. H., Cahill, G. J. *J. clin. Invest.* 1955, **34**, 761.

1. Fular, W., Kraft, E. *Arch. klin. Chir.* 1954, **278**, 548.
2. Fular, W., Kraft, E. *Medizinische*, 1956, **35**, 1197.
3. Krönke, E. *Arch. klin. Chir.* 1956, **283**, 466.
4. Harman, J. W., Ragaz, P. J. *Amer. J. Path.* 1950, **26**, 551.
5. Halasz, N. A., Marasco, J. P. *Surgery*, 1957, **41**, 921.
6. Gold, E. Löffler, E. *Z. ges. exp. Med.* 1923, **38**, 153.
7. Moser, H., Wurnig, P. *Arch. klin. Chir.* 1954, **278**, 72.
8. Whiteley, H. W. *J. Path. Bact.* 1954, **67**, 521.
9. Armin, J., Grant, R. T. *Clin. Sci.* 1951, **10**, 441.

may be attributable to the very small dosage which they employed.

Degrees of pulmonary fat-embolism much more severe than that defined by Armin and Grant as " gross " are not uncommon in man.[10] Certainly these are the cases in which fat-emboli are most likely to spread systemically, but it is also in such cases that changes due to pulmonary embolisation are liable to be erroneously ascribed to the effects of systemic involvement. Although the pathological changes in the lungs—œdema, congestion, and hæmorrhage—are not in any way specific this does not exclude a causal relationship, and in any event the effects of pulmonary fat-embolism may be circulatory as well as respiratory.[11] In my experience a predominantly intra-arteriolar and intra-arterial distribution of fat emboli in the lungs is often associated with a short survival time and an absence of systemic embolisation.[10] Any system of grading the severity of embolisation should take cognisance of the size and situation of the emboli as well as of their numbers.

While the arrest of fat emboli in the pulmonary vasculature undoubtedly protects the systemic circulation it can hardly be regarded as other than a pathological event; I submit that pulmonary fat-embolism should not be entirely discounted as a cause of illness and even death.

University Department of Pathology
Western Infirmary,
Glasgow. A. J. WATSON.

TRIGEMINAL NEURALGIA

SIR,—Professor Dechaume has very kindly sent me two papers [12 13] in which he cites the temporomandibular joint as a potential source of true trigeminal neuralgia. I was unaware of these papers when I wrote my letter of Oct. 1, and I apologise for that omission. Professor Dechaume suggests a method of treatment which is new to me—namely, that the sympathetic enervation of the joint is an effective means of breaking into the vicious circle of effect aggravating cause.

Colchester. MICHAEL FROST.

NICOTINIC ACID IN ISCHÆMIC DISEASE

SIR,—Dr. Archibald's criticism (Oct. 8) of bus-drivers resuming their occupations after a coronary thrombosis is very pertinent, and it was only after very careful consideration that these drivers were allowed to go back to work. Dr. Archibald in effect poses the question: " Should all patients who have had a coronary thrombosis be forbidden for that reason to drive a car?" With the usual treatment, I should be inclined to say " yes ", but I would stress that there is a basic difference with the treatment described in my article of Sept. 24.

It is interesting that Hunter [14] has described results after nicotinic-acid therapy comparable with my own, except that his dosage is smaller; and he concludes that the improvement in angina is maintained so long as treatment is continued, and that angina gradually returns when treatment is stopped. This is in accord with my experience over the fifteen years I have used this treatment, both after infarction and in angina, and it is for this reason that I came to the considered conclusion that ischæmic disease is probably a deficiency disease mainly of nicotinic acid, possibly also of pyridoxine (which forms a coenzyme mediating transaminase reactions and which is probably involved in the enzyme, glutamic-oxaloacetic transaminase). According to this concept, nicotinic acid is a physiological corrective of ischæmic disease.

The first patient cited, who is an insurance agent, tells me he makes more than 100 calls a day in his car, and he has done this now for a long time. The bus-drivers are seen and examined twice a quarter.

Rothwell Haigh,
near Leeds. C. E. GOLDSBOROUGH.

THE VERY DEAF CHILD

SIR,—The complaint of this school, which admits many children who have received various forms of home training, an important aspect of the work of most audiology clinics, is that the period before entry to school for most of them has been inadequately used.

Of the present roll of 40 children, 32 have had preschool help of this kind, varying in length from six months to four years. 30 of these children had hearing-aids issued by the clinics. 2 were deemed too deaf to profit from an aid, though the parents of 1 bought a commercial model.

Of the 31 with hearing-aids, only 4, however, were wearing them correctly—i.e., continuously and at the right setting with an ear-mould which fitted sufficiently well to enable the necessary volume to be reached without acoustic feedback.

At the moment of writing, 21 of the 31 children are wearing their aids properly both in and out of school with corresponding gains in speech improvement and language development. Included in the 10 children who do not reach at home the standard of " hearing-aid usage " expected and obtained from them in school are all the 6 children with multiple handicaps. The remaining 4 are among our most recent admissions.

The fact that so many of these non-hearing-aid-users were trained within a relatively short space to regard their aids as an indispensable ally in their fight against deafness, and not as a barely tolerable encumbrance underlines the need to examine the weaknesses of a form of training which permits so much waste of valuable auditory training time.

No teacher of the deaf, as far as I am aware, disputes the immense value of parent guidance and help to the children, particularly during the period between the diagnosis of deafness and the age of 2–3 years. Many of us, however, believe that a special nursery school, fully equipped and staffed, where parents are free to come and go and take part in our work, where visiting otologists and psychologists can see the children in surroundings more appropriate than the clinical situation found in audiology units, offers not only the well-known advantages of nursery-school training but also permits conditions suitable for full-time educational and audiological help of the kind appropriate to the children's individual needs. In addition, because continuous observation under controlled conditions is possible, it allows a more rapid and accurate assessment of the children's abilities and the nature and degree of their hearing loss, and enables future school placement to be considered on a better-informed basis.

Such a special school should cooperate with local hearing schools for selected activities where the children of both schools can meet and play and, under skilled supervision, work with one another. (This is not difficult to arrange—we do, in fact, work with 3 nearby hearing schools in Woodford in this way.)

Miss Whetnall (Oct. 15) has referred to the work of Wedenberg [1] who, for the initial period of auditory training, applies a live voice to the meatus of the deaf child without the use of an aid. Unfortunately, she omitted to say that Wedenberg himself found that the best subjects for auditory training were the " *gifted children* (my italics) from groups 1a to 2a " (i.e., children with considerable hearing for the important low frequencies, about 50 db. at 250 and 500 cycles) and that children with much less hearing for low frequencies (groups 1b and 2b) were " difficult subjects even when their intelligence is high ".

Of the children here for whom we have reliable audiograms 6 come within Wedenberg's groups 1a and 2a and of these 2 only are of above average intelligence.

Even more significant is the fact that we are able to train children who Wedenberg found " difficult "—i.e., the 1b and

10. Watson, A. J. Fat embolism. Thesis, University of Aberdeen, 1960.
11. Peltier, L. F. *Surg. Gynec. Obstet.* 1957, **104**, 313.
12. Dechaume, M., Dore, M., Le Bars, C., Rouot, J. *Rev. Stomatol.* 1950, **51**, 157.
13. Dechaume, M. *Dtsch. Zahn, Mund- u. Kieferheilk.* 1959, **31**, 69.
14. Hunter, J. D. *N.Z. med. J.* 1960, **59**, 280.

1. Wedenberg, E. *Acta laryngol. Stockh.* 1954, suppl. 110, p. 707.

2b groups " whose sense of hearing is defined as non-functional for the ordinary purposes of life ",[2] into becoming talking children with normal attainments and a good command of language. Only those, however, we have had from a very early age and who have no secondary handicap.

If audiology clinics would transfer to the special nursery school or class at an early age the 1b and 2b children, and those of 1a and 2a group who are not receiving continuous or adequate auditory stimulation either at the meatus or through a hearing-aid, I for one should find less reason for complaint.

Nursery School for Deaf Children,
Woodford Green, Essex. B. I. INGALL.

POTASSIUM IN THE TREATMENT OF CHOLERA

SIR,—In their article last week Dr. Watten and Dr. Phillips suggest that in the treatment of acutely ill patients 10 mEq. (7·5 g.) of potassium chloride should be added to 1 litre of saline solution. The amount in grammes should read *0·75*. This is no doubt a slip, but it is an important one. Owing to the danger that this may be overlooked, libraries might consider making the correction on the article itself.

Radcliffe Infirmary,
Oxford. W. I. CRANSTON.

ADMINISTRATION IN MENTAL HOSPITALS

SIR,—With great respect, I wonder whether Dr. Kidd (Oct. 29) has really found the ideal solution to the problem of medical administration in mental hospitals.

As a medical superintendent, before the advent of the National Health Service and since, I have been trying to find the ideal relationship between the holder of that office and his senior colleagues for thirteen years, but have not succeeded yet, although I do not give up hope.

We have worked a 3-team system here for ten years, and I support wholeheartedly the doctrine of full clinical freedom for all consultants; indeed, my consultant colleagues here have never complained to me of any interference with their work, but much tact and tolerance are needed on both sides if the hospital is to function smoothly as a corporate entity. Dr. Kidd tells us that he is responsible to his management committee for the efficiency of the medical work of the hospital. How does he equate this personal responsibility with the " full responsibility " of his colleagues?

One example will suffice. How would he deal with a situation such as this, which could happen at almost any mental hospital, any day? A fellow consultant admits, as an informal patient, an aggressive psychopath, who then rapes the small daughter of a hospital employee, resident on the estate. I have been in office long enough to know that the Press, the general public, and indeed the management committee will look to one person only for an explanation, and that person is the unfortunate superintendent. It will not help him to say that Dr. So-and-So had " full responsibility ".

The Mental Health Act has defined responsible medical officers as those in charge of the treatment of the patient. Responsible to whom, and for what? Does " treatment " include control of liberty, food, clothing, social and occupational activities, pocket money, and all the many other aspects of a patient's life? If so, the result could be chaos with as many " systems " as there are consultants.

The duties, responsibilities, and powers of medical superintendents have never been clearly defined. No official guidance has been given, presumably in pursuance of the well-known technique of leaving decisions to the man on the spot, with the useful loophole of blaming him afterwards if trouble arises.

Responsibility implies authority to take any necessary action, but the authority of the superintendent is vague in the extreme. Now that consultants, rightly so, are undertaking greater responsibilities, the functions of the medical superintendent are more than ever in need of clarification. This should be done as a matter of urgency, before there occurs some such trouble as that depicted above, with the inevitable recriminations which would follow.

Superintendents have " carried the can " for a long time, but, in a changing world, it would be helpful to know something of its new contents.

Bracebridge Heath Hospital,
near Lincoln. W. A. S. FALLA.

SIR,—Dr. Kidd and his colleagues are to be congratulated on having accepted some of the principles without which a mental hospital continuing to have a medical superintendent can hardly be expected to function efficiently. These are that the medical superintendent should do clinical work and do it on a basis of equality with his fellow consultants, without powers of interference in their work.

I am afraid, however, that Dr. Kidd's exposition of the medical superintendent's position in regard to administration involves apparent contradictions and several false or dubious premises, as exemplified by the suggestion that " as far as the hospital management committee is concerned he is answerable to them for the efficiency of the medical work of the hospital ". I can only think that in this context " answerable " means " responsible " in which case the proposition is quite untenable. A medical superintendent working on a basis of clinical equality with his fellow consultants and without powers of clinical interference cannot be " answerable " for the efficiency of the medical work of the hospital. It is very relevant that the Mental Health Act, 1959, Memorandum on parts I, IV to VII and IX, paragraph 29, describes the " responsible medical officer " as " not responsible or answerable for the patient's treatment to any other doctor ".

Dr. Kidd, having listed various coordinating and facilitating functions of the medical superintendent, all of which, I suggest, can be done as well by the chairman of the medical advisory committee, goes on to say that such work can " perhaps be better done by a man who is permanently appointed to the office, because he has powers of decision and authority not available to an elected chairman of a medical staff committee ". These powers and authority appear to derive from his being " officially recognised as responsible for medical organisation ". This official recognition has the interesting—and highly undesirable—result that hospital management committees "have to take more notice of his monthly reports than the resolutions of medical advisory committees ".

This is precisely the situation which consultants in many mental hospitals are no longer prepared to tolerate, especially in view of the fact that as from Nov. 1 such hospitals will operate on the same basis as general hospitals. All boards of governors of teaching hospitals and the management committees of most general hospitals recognise and " take notice " of their medical advisory committees as represented by an elected chairman. Dr. Kidd has made no case why management committees of mental hospitals should not do the same. Such recognition should be based on the principle that the senior medical staff in any hospital have an equal and shared responsibility for reaching an agreed policy on all administrative matters affecting the hospital as a whole and that the essential administrative work of the medical superintendent or chairman of the medical advisory committee is to facilitate the carrying out of such agreed policy. This may involve difficult negotiations with hospital management committee, regional hospital board, hospital officers, and others. In such situations the

2. *ibid.* p. 19 (reference to the definition issued by the Conference of Executives of American Schools for the Deaf, 1937.)

elected chairman of the medical advisory committee, speaking for the medical staff, *should* carry more weight than a permanently appointed medical superintendent none of whose authority derives from his colleagues.

It will be a pity if the tremendous opportunities for advance offered to mental hospitals by the Mental Health Act are lost by a refusal to accept the above basic principles of hospital administration.

Shenley Hospital,
near St. Albans, Herts. D. BARDON.

OBSTETRIC FLYING-SQUADS

SIR,—Dr. Vartan's letter of Oct. 22 appears to be misdirected, inappropriate and unreasonable. Has no-one ever told him that normal childbirth is a physiological process? To compare it with an operation for varicose veins betrays a distortion of outlook which is all too common.

Hove. F. V. GRIFFITHS.

RADIOCHEMICAL SYNTHESIS OF TRIIODOTHYRONINE

SIR,—Dr. Deutsch (Sept. 10) draws attention to the possible formation of ^{131}I-labelled triiodothyronine by the decay of a molecule of thyroxine containing two ^{131}I atoms, and, with this in mind, discusses the results of Gross and Pitt-Rivers [1–3] and of Braasch et al.[4] His conclusions assume that in these experiments a substantial number of doubly labelled thyroxine molecules is present. Certainly, as regards the work of Gross and Pitt-Rivers, this assumption is incorrect.

The relative numbers of doubly and singly labelled molecules depend on the relative numbers of radioactive (^{131}I) and stable (^{127}I) atoms of iodine present. The position can be more easily illustrated by referring to ^{131}I thyroxine synthesised in vitro by an exchange reaction. In this material labelling can take place in only two atoms, those in the 3′,5′ positions, and not in all four atoms as in the material synthesised in vivo from ^{131}I iodide. Mr. Holloway and Mrs. Pitt-Rivers (Oct. 22) refer to the work of Tata [5] on decomposition products of ^{131}I-labelled thyroxine supplied by Abbott Laboratories. Assuming that this materal is prepared by the method of Gleason,[6] and that it is not diluted with inactive thyroxine after preparation, we calculate, from the quoted maximum specific activity of 50 mC per mg. thyroxine, that 1 mC of ^{131}I is associated with 6·5 μg. of iodine in the 3′,5′ positions. The weight of 1 mC of isotopically pure ^{131}I is 8×10^{-3} μg., and therefore in the 3′,5′ positions of this product 1 atom of ^{131}I is present to approximately 1000 atoms of ^{127}I. This means that for every 2000 singly labelled molecules only 1 is doubly labelled. No detectable amount of ^{131}I-labelled triiodothyronine is therefore likely to arise by the process postulated by Deutsch, and the fact that no ^{131}I-labelled triiodothyronine was detected in Tata's work gives us no information on the correctness or otherwise of Deutsch's postulate.

The position regarding in-vivo syntheses is more complex. Inactive iodine may be present in the so-called "carrier-free" ^{131}I iodide, and dilution with further inactive material may take place during transport in the body to the thyroid gland, and in the thyroid gland itself. Before 1954, ^{131}I produced in Great Britain had a specific activity of about 1 mC per μg. iodine: this implies that about 1 in every 100 atoms of iodine present was radioactive. It was this material that was used in the work of Gross and Pitt-Rivers. Even had no further dilution taken place in the subjects the number of multiple (i.e., double, triple, or quadruple) labelled molecules would be too small to yield a significant amount of ^{131}I-labelled triiodothyronines by decay (assuming that ^{131}I atoms are randomly distributed in the 4 positions of thyroxine, multiple-labelled molecules would form about 1·5% of the total labelled molecules).

The specific activity of ^{131}I produced in Great Britain has increased markedly since 1954. The Radiochemical Centre product is specified as being not less than 10 mC per μg. iodine, and individual batches have given 20 mC per μg. iodine: this latter figure corresponds to 1 atom of ^{131}I in 6 atoms of iodine. The proportion of ^{131}I atoms in fission product ^{131}I supplied by Oak Ridge is probably even higher. Rupp et al.[7] suggest 1 atom of ^{131}I to 1 atom of ^{129}I plus ^{127}I (^{129}I is sufficiently long lived to be considered stable). With material of such high specific activity any dilution with stable iodine in the body before thyroxine synthesis becomes specially important. The factors determining the extent of such dilution are too complex for discussion other than by an expert in the field. In general it seems reasonable to suppose that the extent of dilution will be relatively large. In certain cases this may not be so, and ^{131}I-labelled triiodothyronine might arise in the manner postulated by Deutsch.

Radiochemical Centre,
Amersham. J. C. CHARLTON.

1. Gross, J., Pitt-Rivers, R. *Lancet*, 1951, ii, 766.
2. Gross, J., Pitt-Rivers, R. *ibid.* 1952, i, 439.
3. Gross, J., Pitt-Rivers, R. *Biochem. J.* 1953, **53**, 645.
4. Braasch, J. W., Flock, E. V., Albert, A. *Endocrinology*, 1954, **55**, 768.
5. Tata, J. R. *Clin. chim. acta*, 1959, **4**, 427.
6. Gleason, G. I. *J. biol. Chem.* 1955, **213**, 837.

PERITONEAL SPLASH: A PHYSICAL SIGN

SIR,—Mr. F. G. Smiddy (Oct. 15) points out that this physical sign can be elicited only in the anæsthetised patient. Many years ago, when I saw more patients with perforated peptic ulcer than I do now, I noticed that in some it was possible to detect a splash while percussing for free gas in the peritoneal cavity. Light and careful percussion in the line of the right nipple with the patient prone will in many cases reveal the gas bubble which obliterates the band of dullness over the liver. At the lower edge of the bubble the pleximeter finger detects a faint splash as the abdominal wall comes into contact with the surface of the fluid behind the bubble. This sign is easily elicited when the perforation is large, there is much effusion in the peritoneal cavity, and the rigidity of the abdominal wall is less than board-like. But then the diagnosis can more confidently be made by other means. In the early case with a small hole, little effusion, and a rigid abdominal wall the sign is not easily elicited.

I concluded that as a physical sign it was of little value, but when present it provided a comforting confirmation of the diagnosis.

Whiston Hospital,
Prescot, Lancs. J. A. MARTINEZ.

SIDE-EFFECTS OF LIBRIUM

SIR,—I read with close attention the correspondence that followed the letter by Dr. Ingram and Dr. Timbury (Oct. 1) about the new drug methaminodiazepoxide ('Librium').

My mind was certainly imbued with that attitude of scepticism and circumspection favoured by your correspondents when I first prescribed these capsules for patients with anxiety states, since I had seen in recent years the much-vaunted advent of a glut of new drugs, the great majority of which were destined to find ere long a dusty tomb on some neglected shelf of the dispensary. I soon came to the conclusion, however, that librium is of much value in the anxiety states. Considerable benefit was obtained in some 5 out of 10 sufferers from morbid anxiety, a result which was the more impressive because not a few of them had previously had little or no relief from other calmative drugs—which clearly mitigates the influence of suggestion. A large majority of those responding to the drug need take the relatively modest dose of 10 mg. three times daily to gain relief from their emotional tension, disagreeable side-effects being exceptional in such

7. Rupp, A. F., Beauchamp, E. E., Farmakes, J. R. United States Atomic Energy Commission document ORNL-1047. Production of Fission Product Iodine 131.

circumstances. Some of these patients remarked that, unlike other drugs they had tried, librium suppressed their anxiety without producing troublesome somnolence. In my hands, the drug has proved more useful for the assuagement of diffuse anxiety than for the relief of the specific phobias of the obsessional neuroses.

Although it would doubtless be prudent to postpone *final* judgment I am confident that this drug will soon win its spurs in general practice, and thereby materially reduce the number of cases of anxiety state referred to psychiatric out-patient clinics.

Menston Hospital, Ilkley, Yorks. J. TODD.

HEPATIC SIZE, SHAPE, AND CONTENT

SIR,—We must be grateful for having been reminded of the advantages of peritoneoscopy. Though too seldom practised in this country, its value in the diagnosis of hepatic disease and anatomical abnormalities must be recognised.

For the certain exclusion of disease, however, it is not so reliable, and this and its other limitations seem to me to indicate the desirability of laparotomy in determining that no hidden metastases are present in the liver.

Churchill Hospital, Headington, Oxford. C. GRIMSHAW.

NEGATIVE ASSOCIATION OF ABO BLOOD-GROUPS WITH FRACTURED HIP

SIR,—In your issue of Aug. 13, Dr. Wiener said that Buchwalter had observed an excess of blood-group A in patients with fractured femurs. We note that Buchwalter [1] has investigated the ABO blood-group distribution in 910 cases of fractured hips and found no statistical difference when compared with a control group. We have examined a small series of patients who had been treated for fractured femoral necks at this hospital. All these patients had been blood-grouped on admission as a matter of routine.

TABLE I—ABO BLOOD-GROUP DISTRIBUTION

Group	Control series	Intertrochanteric fracture group	Other femoral neck fractures	Total test series
A	1906 (32·3%)	56 (42·8%)	73 (33·5%)	129 (37·0%)
B	637 (10·8%)	9 (6·9%)	22 (10·1%)	31 (8·9%)
AB	178 (3·0%)	2 (1·5%)	6 (2·7%)	8 (2·3%)
O	3177 (53·9%)	64 (48·8%)	117 (53·7%)	181 (51·8%)
Total	5898	131	218	349

TABLE II—DISTRIBUTION OF THE RHESUS FACTOR

Rhesus	Control series	Fracture series
Positive	344 (80·6%)	279 (79·9%)
Negative	83 (19·4%)	70 (20·1%)
Total	427	349

Table I shows the ABO groups of these 349 patients and those of the control series compiled from data from 5898 consecutive new donor registrations with the West of Scotland Regional Blood Transfusion Service. The patients were further subdivided into intertrochanteric fractures and other femoral neck fractures. This small series reveals that there is no significant difference in ABO blood-group distribution; although one may be impressed by the relatively high incidence of group A in the intertrochanteric fracture group, there is no statistical difference ($\chi^2=1{\cdot}3$). Furthermore, table II shows that there is again no significant difference in the incidence of the rhesus factor in the fracture patients and those of a small control series of 427 donors.

1. Buchwalter, J. A. *Acta genet.* 1957, **6**, 561.

We wish to thank Dr. I. A. Cook, Mr. W. Sillar, and Dr. J. Wallace for assistance, and Dr. R. A. Robb for his statistical help.

Southern General Hospital, Glasgow. J. MALCOLM CAMERON
A. G. MELROSE
G. A. WHITEFIELD.

MODERN CLINICAL BIOCHEMISTRY

SIR,—Professor Cappell's presidential address (Oct. 15) has called forth a prompt and explosive comment (Oct. 29, p. 985) from his biochemical colleague at the Western Infirmary.

As a biochemist, Dr. Hendry is naturally most concerned with Professor Cappell's assessment of the position of chemical pathology in the framework of clinical pathology, and there can be little doubt that he has voiced the feelings of many of the medical and non-medical biochemists who have entered or considered entering the hospital laboratory service. These feelings are clearly expressed in their reluctance to apply for posts. If Dr. Hendry as the head of a teaching-hospital biochemistry department can say it is all but impossible to recruit young science graduates into hospital biochemistry departments, how much more so is this the case in regard to the non-teaching hospitals administered by regional boards, and this at a time when scientists are making fundamental contributions in every branch of industry and many other fields of activity. Why should the hospital service alone be denied this advantage? Surely the health of the nation should have at least an equal call on the scientific potential. No medical man can view this situation with equanimity, and least of all pathologists whose own work can gain so much more significance and value by close collaboration with chemical studies. It would seem worth trying to find the explanation for the unpopularity of hospital work for science graduates.

Firstly, the newly graduated chemist, if he is worth his salt, will wish to advance his knowledge and status by acquiring a postgraduate qualification. This requires in the case of a PH.D. that the department in which he works will be recognised by a university department of chemistry or biochemistry as giving proper facilities for postgraduate study together with supervision by a senior member of the staff of these departments. In the case of an M.SC. no university supervision is required, but unless the proper facilities are there the preparation of a thesis will be impossible. These facilities consist above all in adequate time—and, in the case of more senior biochemists, assistance—to pursue a research project, and there seems no doubt that the greatest drawback to the hospital biochemistry service in the eyes of would-be graduate recruits is the lack of time and encouragement to undertake research. Many pathologists consider biochemical research inappropriate in hospital laboratories, especially in non-teaching hospitals, or, even if they are convinced of its value, are unable to persuade hospital management committees to provide sufficient staff to enable the biochemical graduate to devote time to original investigations. He is consequently inundated with routine and repetitive work and soon becomes dispirited and leaves the service, or stays on disgruntled with a grudge against doctors in general and pathologists in particular.

No greater catastrophe could befall the pathologist than to lose that intimate contact with the biochemist which promises to solve many problems which neither can solve alone. Yet it is clear from Dr. Hendry's letter that the pathologists' laudable attempts to weld the hospital

laboratory disciplines into a single integrated team are viewed with the greatest suspicion by medically and non-medically qualified biochemists alike. The reason for this lies in the question of prospects. The young biochemist is not going to sit back and vegetate when he has obtained his postgraduate qualifications. He hopes eventually to attain as senior and respected a position in the hierarchy of the hospital staff as he would in industry or other Government scientific establishments, and to have a reasonable chance of running his own department. Under the present circumstances he will find his way blocked in both these directions. He cannot obtain status comparable with his medical colleagues as long as his method of appointment is that of registrars, technicians, and radiographers—viz., by hospital management committees and not by regional boards. Neither can he obtain it—human nature being what it is—as long as his salary is so much less than that of his medical colleagues that he cannot join fully with them in social activities and educate his children similarly. As for running his own department, it is generally believed that the Association of Clinical Pathologists considers that the biochemist should be directly responsible to the head of the laboratory in which he works (i.e., the senior clinical pathologist), though I am not aware of any published statement of this policy. While not suggesting that a non-medical biochemist should be in charge of the other clinical pathological laboratories, I am at a loss to see why a senior biochemist, whether medical or non-medical, should not be in absolute charge of his department, responsible only to the employing authority. Of course there will be many matters of a clinical nature which he will want to discuss with the medical pathologists, but surely discussion on terms of parity is the essence of the teamwork which we wish to see in the integrated department of clinical pathology of the future.

Yet another explanation for the mistrust by biochemists of pathologists lies in the manner in which the latter are organised for political purposes. The Association of Clinical Pathologists has only medically qualified full members. How can it be representative of biochemists in general? If it wishes to be considered thus representative, it must give full membership to all hospital biochemists of suitable seniority (which would seem appropriate enough if hospital biochemistry is indeed a branch of clinical pathology!). Similarly if pathological advisory committees wish to be considered qualified to advise regional boards on biochemical matters they should admit senior non-medical biochemists to membership. If these suggestions are not attractive to pathologists, would it not be better for them to leave the advising on biochemical matters to the Association of Clinical Biochemists on the one hand and to regional biochemistry advisory committees, still to be formed, on the other? While retaining their role of principal advisor to the authorities on biochemical matters, these organisations would no doubt welcome and benefit by periodic discussions through joint consultative committees with the corresponding pathological bodies.

In the meantime, the recruiting position has deteriorated to a stage where it is impossible to fill biochemical appointments even with candidates who are far from ideal. There is here a vicious circle. The poor quality of the majority of science graduates accepting posts in the hospital biochemistry service has prevented many pathologists from gaining insight into the reliability and potentialities of the best type of biochemist. Otherwise it is possible that a far greater degree of responsibility and scope would have been accorded the science graduate. Now it is too late, and in despair the pathologists have turned to the young men of their own profession to fill the gap. Although there is much that is attractive in the medically qualified biochemist (chemical pathologist), the disadvantages would seem far to outweigh the advantages if he is only going to have one year of fundamental study in chemistry as Professor Cappell suggests. With so little experience in chemistry, how will he be able to attract to work under him keen young scientists just leaving university departments of chemistry four years after they have taken their advanced level G.C.E.? If he does not attract them, the standing of our departments of chemical pathology will fall below those of departments of clinical chemistry in other countries.

I would suggest it would be far more long-sighted to make the hospital biochemical service attractive to the best young brains in chemistry and biochemistry by introducing the following innovations:

(*a*) Every biochemist post advertised (or at least a considerable proportion, which should be specially designated as largely free from routine and repetitive work) should carry with it: (i) facilities for obtaining a postgraduate qualification; (ii) reasonable opportunity to reach status comparable in salary and independence with that of medical consultants;

(*b*) Research should be considered a normal and not an exceptional activity of biochemistry departments.

(*c*) Appointments to senior (principal and top-grade) biochemical posts should be made by regional boards.

(*d*) Biochemistry advisory committees should be appointed by regional boards and should always include a professor of chemistry or biochemistry.

Although there are many other ways in which hospital biochemistry could be made more attractive, if those mentioned here are implemented there would surely be a most gratifying influx of the best type of scientist into the service, and I should like to see pathologists taking the lead in securing these improvements because it is they who will gain most by having the privilege of working as a team in close collaboration with the finest products of our universities' scientific departments.

Midland Centre for Neurosurgery,
Smethwick. A. L. WOOLF.

CHROMOSOME ANALYSIS

SIR,—I was surprised by Dr. Stewart's letter of Sept. 17. From his statements, one may conclude that colchicine and its derivatives causes heteroploidy and triploidy in animals. So far as I am aware, the few cases of heteroploidy and triploidy observed in animals were associated with a highly artificial technique.

Colchicine was added to sperm material and the animals artificially inseminated. In this way, a few rabbits and one pig supposed to be triploids were obtained.[1,2] However, the accounts concerning these animals have been criticised and their triploid nature is unconvincing and not yet established.[3] To sum up, it is apparent from these reports that no polyploid animals have been produced by colchicine.[4] Moreover, colchicine does not cause gene mutation.[5]

Recently, by intrauterine injections of colchicine into female mice just before mating, Edwards obtained some heteroploid embryos at $3^1/_2$ days' gestation. Chromosome counts of the mature offspring of these females, however, showed no heteroploids.[6] Using a different technique, similar results were obtained in rats by French workers. A few "heteroploid" embryos were seen at 12th day but none at full-term gestation.[7]

The method is, I believe, simple and useful. The results are good, and nothing suggests that the intravenous administration of the colchicine derivative is

1. Melander, Y. *Hereditas*, 1950, **36**, 335; *ibid.* 1951, **37**, 288.
2. Häggkvist, G., Bane, A. *ibid.* 1950, **36**, 329.
3. White, M. J. D. Animal Cytology and Evolution. Cambridge, 1954.
4. Eigsti, O. J., Dustin, P., Jr., Colchicine. Iowa, 1957.
5. Dobzhansky, T. Genetics and the Origin of Species. New York, 1941.
6. Edwards, R. G. *J. exp. Zool.* 1958, **137**, 317; *ibid.* p. 349.
7. Piko, L., Bomsel-Helmreich, O. *Nature, Lond.* 1960, **186**, 737.

dangerous. So far we have used the drug in 62 patients without any toxic manifestation.

Department of Clinical Medicine,
Medical School of Ribeirão Prêto,
São Paulo, Brazil.

CÁSSIO BOTTURA.

TREATMENT OF IDIOPATHIC HYPERCALCÆMIA OF INFANTS

SIR,—Many articles have now appeared about the treatment of idiopathic hypercalcæmia of infants. A low calcium and vitamin-D intake, a high phytate intake, and the administration of cortisone have been recommended. To my knowledge mention has not been made of the possible beneficial effect of total exclusion from ultraviolet rays.

The antirachitic effect of sunlight is thought to be due to the activation of 7-dehydrocholesterol in skin. This activation may result in the formation of substances with vitamin-D activity equivalent to 1000 or more units of vitamin D per day in infants who are exposed to ultraviolet radiation. Possibly this disease has not been reported in Negroes because of the lesser effect of ultraviolet rays on deeply pigmented skin.

It seems probable that infants with idiopathic hypercalcæmia are sensitive to very small amounts of vitamin D and it would seem advisable that patients with this disease be excluded from sunlight during those seasons when rays between 280 and 320 μ are present.

Possibly someone with knowledge of the metabolism of vitamin D might render judgment whether infants with idiopathic hypercalcæmia should be excluded from sunlight as part of their treatment.

Department of Pediatrics,
Jefferson Medical College,
Philadelphia.

HANS G. KEITEL.

TREATMENT OF OBESITY BY THE HIGH-FAT DIET

SIR,—Bearing in mind case 5, and the large group of patients and friends she appears to represent, can Prof. Yudkin and Miss Carey (Oct. 29) offer a 1500-calorie diet that is *permanently* acceptable both *socially* and financially to an adult woman of any age? An overweight woman is conspicuous in a crowd: she does not wish to draw further attention to herself by always differing from the group when she is not eating alone.

We would be most grateful.

Hadleigh, Essex.

DAPHNE SASIENI.

ERYTHROCYTE ENZYME DEFICIENCY IN UNEXPLAINED KERNICTERUS

SIR,—I was very interested by the contributions from Smith and Vella [1] and Doxiadis et al.[2] They confirm some observations I had the opportunity to report [3–6] last year.

I have so far studied 19 jaundiced newborn children (11 males, 8 females) with unstable G.S.H. and/or G.-6-P.D. defect in their erythrocytes. In 10 cases exchange transfusion was performed: 7 of the transfused children and none of the untreated survived without damage. Precipitating factors, such as dangerous drugs, were recognised in only a few cases. Severe anæmia was rarely present; on the other hand, jaundice was often associated with severe clotting disturbances, indicating perhaps hepatic impairment, which may be due to the enzyme abnormality itself. In fact, as I was able to demonstrate by liver biopsy, G.-6-P.D. activity is decreased in the liver of sensitive individuals as well as in their erythrocytes.[6]

The observations of Smith and Vella and Doxiadis et al. emphasise again the importance of this particular type of neonatal jaundice. They also confirm the high incidence of the syndrome in a few families bearing the defect; and this fact suggests that there is a genetic factor in addition to the G.-6-P.D. defect.

Clinica Pediatrica,
Università di Sassari,
Italy.

FRANCO PANIZON.

A SEVERE ANAPHYLACTOID REACTION TO HYDROCORTISONE

SIR,—Occasional allergic reactions following the local injection of hydrocortisone have been recorded,[1] and in many cases the possibility that associated use of hyaluronidase or procaine was to blame has not been firmly excluded. The following case illustrates an allergic response of alarming severity to the injection of 'Hydrocortisyl' (Roussel) 5 ml. in a patient who had never had either local or general steroid medication.

No other solution was injected and it was possible to exclude any previous injections (within 2 months) and any tablets or medicines (except 2 tab. codein. co. *B.P.*, to which the patient was accustomed, taken a week previously). Similarly no dietary explanation could be discovered.

A woman of 50 had, on April 8, 1960, a cup arthroplasty for osteoarthritis of the right hip. She made a normal recovery, and was discharged to outpatients on June 17.

On Sept. 15, during follow-up examination, she complained of pain in the right shoulder. A typical moderately severe supraspinatus tendinitis, with early pericapsulitis, was found, and at about 3.30 P.M. hydrocortisyl 5 ml. was injected into the rotator cuff.

She had no immediate ill effects, but at 7.30 P.M., after supper, she suddenly felt her "face funny—blotchy with lumps, and burning". Red patches appeared on her arms, and she felt sick. She "passed out" and was carried to bed.

An hour later, when her doctor arrived, she had regained consciousness, but she was vomiting profusely, had pain in the stomach and loins, and had urticaria, especially on the arms and face. Conglomerate petechiæ and bruises appeared over the arms and face. She was in a state of shock, with tachycardia, extrasystoles, and a weak pulse. There was much abdominal tenderness, especially in the liver area.

She was given anti-histamines ('Piriton'), and she felt a bit better next day, but for 2 days she vomited repeatedly and had diarrhœa and rectal incontinence. The stools were fluid and black, and the vomit contained dark blood.

She was readmitted to hospital on the 3rd day. Laboratory investigations showed: hæmoglobin 92%, platelets 300,000 per c.mm., bleeding-time 2 min., clotting-time 6 min., clot retraction after 1 hour normal, prothrombin content 100% of normal, and prothrombin consumption normal. The vomit contained dark blood, and occult blood was present in the stools. The urine was normal.

Vomiting and diarrhœa ceased on the day of admission, and the abdominal pain and tenderness cleared up within 48 hours. She returned home after 5 days.

Although intradermal skin tests were unlikely to be helpful so soon after such a severe reaction, they were attempted on Sept. 7 using: (1) control solution; (2) a minute dose of penicillin (to exclude penicillin contamination of the syringe used for injection); and (3) hydrocortisyl 0·01 ml. An erythematous plaque 0·75 cm. in diameter formed in 24 hours around the site of hydrocortisyl injection, and persisted for 2 weeks, while the control sites showed no reaction.

Thus it appears almost certain that this alarming reaction was due to the hydrocortisyl injection. Some

1. Smith, G., Vella, F. *Lancet*, 1960, i, 1133.
2. Doxiadis, S. A., Fessas, P., Valaes, T. *ibid.* July 2, 1960, p. 44.
3. *Studi Sassaresi*, 1959, **37**, 19.
4. *Acta pædiat. latina*, 1959, **12**, 904.
5. XVII Congrès des Pédiatres de Langue Française; Oct. 1959, vol. IV. Montpelier.
6. *Boll. Soc. Ital. Biolo. Sper.* 1960, **36**, 106.

1. Kendall, P. H. *Ann. phys. Med.* 1958, **4**, 170.

2000 hydrocortisyl injections have been given in this department over the past 3 years, and except for one case of mild infection following an injection for tennis elbow no other ill effects have been encountered from the use of these injections for the minor orthopædic troubles treated by this method.

My thanks are due to Dr. Josef Grutz, who dealt with this emergency so capably, and who has cooperated in the inquiry concerning ætiological possibilities.

Oldchurch Hospital,
Romford, Essex. R. A. KING.

ZOLLINGER-ELLISON SYNDROME

SIR,—With great interest I read the article in your issue of July 16 concerning this syndrome with diarrhœa and malabsorption. The gastric-secretion studies before and after removal of the pancreatic islet-cell tumour were particularly striking. As the Birmingham group point out, confirmation of their observation with tumours of similar type is important, so you may be interested in the story of a patient Dr. G. J. Verdonk and I reported [1] at a colloquium of gastroenterology in Antwerp in September, 1958.

A 66-year-old woman who presented herself in June, 1957, had a continuous pain in the epigastrium, spreading to the back. After meals the pain was worse and she complained of heartburn and eructation. She had no diarrhœa—on the contrary there was a distinct constipation. She never had hypoglycæmic attacks.

Examination of this fat healthy-looking woman revealed a resistance in the left upper abdomen which was at first thought to be an enlarged spleen.

Erythrocyte-sedimentation rate 15 mm. in one hour. Hæmoglobin 12·8 g. per 100 ml. White cells 5400 per c.mm., normal differential count. Liver-function test normal. No occult blood in the fæces. Urine normal. A fractional test-meal showed considerable hyperacidity: free acid 106, total acid 120.

X-ray examination of the stomach did not demonstrate an ulcer, but the mucous-membrane pattern was rough. On compression of the stomach an area of lack of contrast was visible, possibly caused by pressure from behind. The radiologist suggested a pancreatic tumour or cyst. Just distal to the duodenal bulb a pseudopodial contour was seen, interpreted as a diverticulum.

After six weeks' ulcer treatment with rest, diet, antispasmodics, sedatives, and antacids she was admitted to hospital, because the abdominal mass was still palpable. We finally decided on operation. On Nov. 1, 1957, a pancreatic tumour, $7 \times 6{\cdot}5 \times 6{\cdot}5$ cm., was removed. During the operation the stomach and intestines could not be explored. The surroundings of the tumour and omentum were hyperæmic and contained large dilated veins. The omentum was containing the tumour and was firmly connected to the surface of the spleen. The tumour was removed without vagtomy or gastrectomy. The histological diagnosis was " insulinoma ".

In September, 1958, nearly ten months after the operation, a fractional test-meal showed that the acid secretion was now reduced to subnormal: free acid 0, total acid 16 (maximum).

Municipal Hospital,
Arnhem, Holland. M. DIJK.

1. Dijk, M., Verdonk, G. J. *Tijdschr. Gastro-enterologie*, 1958, **1**, 481.

The Widdicombe File

LXVII.—THE DIVISION OF PATHOLOGISTS

DEAR PETER,

I too thought your letter was sound but I think your friend G.G., like several of the pathologists, is not entirely familiar with the real function of a college. They ask " Can we trust the physicians ", meaning presumably the internists, the dermatologists, the pædiatricians, the neurologists, the psychiatrists, and the other *clinicians* in the college, and they talk earnestly about the need for independence. But, bless our souls, why do they need to be independent? A college is basically a degree-granting body and also ideally a community of individuals with kindred interests. Do we hesitate to take a university medical degree because we doubt the good intentions of the philosophers or theologists who are represented in its court, or do we demand independence so as not to have to eat at table with engineers or lawyers? Maybe the young men want independence at any price because this is the parrot cry of the mid 20th century. Fortunately in the college the dermatologists seem to show no distrust of the psychiatrists, and the neurologists are not afraid of being outvoted by the general physicians else there would have to be lots of new colleges. What will it benefit the pathologists of tomorrow to have their own college with its expensive library and regalia, portraits and plate? Are pathologists anxious to accept the social and other obligations of a college and to maintain an expensive establishment—for rest assured they will not for long remain content with an attic in Euston but will feel the urge to compete on the perimeter of Regents Park?

Although your arguments were sound one correspondent accused you of talking nonsense. His letter reveals the lack of cohesion amongst pathologists and indeed the seed of the next potential split (" Can we consultant biochemists trust the pathologists and bacteriologists?—we must be independent at all costs "). What I mean is this, Peter, if the pathologists (and I am using this term generally to include bacteriologists, virologists, chemical pathologists, serologists, forensic pathologists, and hæmatologists—all in fact who are concerned with the laboratory investigation of the patient alive or dead) do not accept this very generous offer of negotiation by the Royal College of Physicians (some claim that it will fail because it is too generous), they may have to wait a long time before achieving the unanimity they require to embark on a new venture. Many of the academic pathologists—if what I hear is true—care little whether there is a faculty of the college or a new college.

Please impress on your many pathologist friends, Peter, that a faculty will require an appreciable measure of support but a new college will require overwhelming support from all species of pathologists. Remind them that a faculty can always be dissolved (I trust that in the event of a faculty both the pathologists and the college will insist on having this in their agreement) but once they embark on a college they will have committed their successors to a life of independence and will have severed connection with their clinical colleagues. A recent president of the college, it is said, once invited the pathologists to look forward fifty years. They should do this now. The rapid growth of specialism, automation, and the increasing excellence of technicians may bring the pathologist of the future much nearer to the patient than he is today and nearer to the clinicians. An irrevocable move at this time would be a misfortune.

Yours ever,
W. W.

Parliament

Queen's Speech

In the Speech from the Throne at the opening of Parliament on Nov. 1 it was announced that the Government proposed to increase war pensions, and retirement pensions, other benefits, and contributions under the National Insurance schemes.* They would authorise an increasing level of expenditure on the physical recreation of the young. Awards for students at universities and for those taking comparable courses at other institutions of higher education would be granted on an improved basis. They would introduce a Bill to provide better means of dealing with young offenders; to extend compulsory aftercare to prisoners and so to discourage them from reverting to crime; and to improve the management of approved schools.†

Welsh Teaching Hospital

On Nov. 2, on the adjournment, Mr. LEO ABSE sharply criticised the plans for this new teaching hospital, which he described as an "ossified hospital design accepted from a septuagenarian architect by assessors led by another septuagenarian architect . . . a design for a hospital for 1950, not as it should be for a 1980 hospital". Wales wanted a forward-looking teaching hospital; it was being proffered a mausoleum.

Going on to offer detailed criticisms, he said that the contemptuous attitude to research was well illustrated by the location and space allocated to the animal house. In defiance of hospital planning, the X-ray department was so embedded within the building that expansion was well nigh impossible. A derisory amount of space was allocated for radioisotopes. A trivial 32 beds had been allocated to mental illness, and there was still no sign of a department and chair in psychiatry being created. But the most dismaying feature was the ludicrous amount of space allocated for research in relation to bed space. The design gave every appearance of there having been a battle for beds between heads of departments.

Other points which he made were: quiet rooms in the noisiest part of the building; the sluice room farthest from the beds most needing its services and unrelated to treatment suite; cross-infection risks increased by infected material being brought into the ward suite for disposal and by inadequate air-conditioning; lavatories concentrated in blocks and not related to bed areas or day spaces; an operating-theatre with a wood-block floor which could never be sluiced clean; eight-storey light wells which meant that wards would be badly lit and have a wretched outlook.

All these blunders and many more, he added, would be housed in a dull cliff-like bulk of buildings unmistakably institutional in appearance.

Miss EDITH PITT, the parliamentary secretary to the Ministry of Health, welcomed the opportunity of discussing the University Hospital of Wales and of replying to some of the criticisms. The fact that it was an undergraduate medical school dictated not only the concept of the work to be performed there but also the site of the hospital, which was to have 650 beds. The scheme must be viewed against the development of acute hospital services in South Wales, which included not only another major acute regional hospital working in the Cardiff area, but also major acute hospitals at Bridgend, Pontypridd, and Newport, and others in the Welsh Hospital Board's plans for Merthyr and North Monmouthshire.

The Board of Governors of the United Cardiff Hospitals and the Welsh National School of Medicine desired a hospital integrated with a medical school, with the closest possible working arrangements between the professional and the clinical staff and with the various departments and their research and other laboratories. An architectural competition for an important scheme of this size was thought preferable to selecting an architect, because it was believed that competition would give incentive to a number of architects to think about the problems set by the promoters, and that new ideas and techniques might be evolved. Competition, however, could do no more than select an architect and, in a scheme of this size, a fundamental design. The promoters and architect could deal with each other on paper only in broad outline. The details must wait till later. A series of working parties had now been set up to go into the plans of the various units with the architect and with the engineer.

Ward units, outpatient department, lifts and communications, catering and food distribution, training accommodation, the dental school, were all being looked at in this way. The internal design and layout of the ward unit, for instance, had already been replanned to provide better access and better supervision, to take account of the latest thoughts on cross-infection; more single rooms had been provided, and the large ten-bed unit had been broken up into smaller units.

This was a normal process which one would expect to take place with any design, and similar replanning was going on throughout the hospital. The promoters had examined the design carefully in the light of the numerous criticisms and were satisfied that the completion of the process of preparation of detailed sketch plans, which was now going on, would give them a modern and efficient hospital and a medical teaching centre. She thought it premature at this stage to be too critical of the detailed planning because the details had still to be filled in. It was her earnest hope that, when this hospital was completed, the Welsh people would have a hospital in accordance with their wishes and a hospital of which they might be proud.

QUESTION TIME

Poliomyelitis Vaccination

At Sept. 30, 13,333,000 people in England and Wales had been vaccinated against poliomyelitis under the National Health Service.

* Details of these proposals are given on p. 1081.
† Details of these proposals are given on p. 1082.

Appointments

BIRKBECK, M. Q., M.B. Cantab., D.PHYS.MED.: consultant in physical medicine, Northampton/Kettering area.
BROWNE, M. P., M.B.E., M.B. N.U.I., D.T.M. & H.: airport M.O., health control unit, London Airport.
BURTLES, RICHARD, M.B. Lond., F.F.A. R.C.S.: consultant anæsthetist, Northampton and Kettering area.
EMERY, RALPH, M.B. Lond., M.R.C.P.E., D.P.M.: assistant psychiatrist (S.H.M.O.), Aylesbury and High Wycombe area.
ETON, BRUCE, M.D. Manc., M.R.C.O.G.: S.H.M.O., maternity hospital, Cambridge.
LUNN, J. E., M.B. Glasg., D.P.H., D.P.A.: assistant M.O.H. and assistant school M.O., Oldham.
ORTON, W. T., M.B. Belf., D.P.H.: senior assistant M.O., Wembley and Willesden.

Birmingham Regional Hospital Board:

BATTEN, R. L., F.R.C.S.: consultant surgeon, West Bromwich group of hospitals.
GALLA, THOMAS, M.B. Edin., D.P.M.: consultant and deputy medical superintendent, St. Edward's Hospital, Cheddleton and Stoke-on-Trent hospital group.
HILL, EILEEN E., M.D. Glasg., M.R.C.P., D.C.H.: consultant pædiatrician, Birmingham (Selly Oak) hospital group.
ROBB, H. P., M.B. Aberd., D.P.M.: consultant psychiatrist and deputy medical superintendent, Lea Hospital and Lea Castle Hospital.
ROSS, J. H., M.D. Cantab., M.R.C.P., D.OBST.: part-time consultant physician, Herefordshire hospital group.
SAGE, R. H., M.B. Birm., F.R.C.S.: consultant surgeon, Birmingham (Selly Oak) hospital group.

Liverpool Regional Hospital Board:

OSWALD, D. C., M.B. Dubl.: assistant pathologist, Birkenhead H.M.C.
PORTER, R. A., M.B. Belf.: deputy medical superintendent (S.H.M.O.), Moss Side Hospital.
SNOW, R. G., M.B. Birm., F.F.A. R.C.S.: part-time consultant anæsthetist, Chester area.

Manchester Regional Hospital Board:

FLEMING, A. C., M.B. Durh., D.P.M.: consultant psychiatrist and medical superintendent, Calderstones Hospital, Whalley, near Blackburn.
GRIMSHAW, LINTON, D.F.C., M.B. Manc., D.P.M.: consultant psychiatrist, Bury and Rossendale hospital group.
KRAWIECKI, J. A., M.B. Edin., D.P.M.: consultant psychiatrist, West Manchester and Springfield and Swinton hospital groups.
METCALFE, W. J., M.B. Manc., F.R.C.S.: consultant surgeon, Blackburn and district hospital group.
SIMPSON, D. C., M.B. Edin.: senior casualty officer, Withington Hospital, near Manchester.

Obituary

JAMES ERIC PATERSON

M.B. Glasg., F.R.F.P.S.

Mr. J. E. Paterson, honorary consultant in neurosurgery to the Scottish Western Regional Hospital Board, died at his home in Rothesay on Oct. 26.

He was the son of a doctor and graduated from Glasgow University in 1911 as the most distinguished student of his year. He spent some years in resident hospital posts, in general practice, and in junior staff appointments in surgery, gynæcology, and anæsthetics before he joined the R.A.M.C. to serve in France during the first world war. After the war he returned to general practice and part-time specialism, and in 1920 was elected F.R.F.P.S.

In 1926 he was offered the post of visiting surgeon to Stobhill Hospital, Glasgow, at that time a poor-law institution with 2000 beds for the aged and the chronic sick. This appointment required him to give up general practice but gave him no chance to build up a consulting practice, and its acceptance meant a considerable financial loss. A colleague relates:

"To be poorly paid for tending the 'dregs of humanity' was no deterrent to this extraordinary little man. From the apparent dross he extracted much gold and gained a breadth of experience which few have achieved. To suit his poor-risk patients he developed multi-stage operations. He quickly learned the need for meticulous preoperative preparation and postoperative care and set up a specialised anæsthetic service. In the early '30s his was a lone voice preaching the gospel of biochemistry, and he used the, then, slight resources of that science to the full. Blood-transfusions were commonplace in his work when they were seldom thought of elsewhere, and before the late war there was a blood-bank in Stobhill.

"He was indeed a general surgeon, whose work ranged from the newborn to the geriatric patient and embraced all specialties. His technique was superb. Watching him operate was like turning the pages of a beautifully illustrated atlas of operative surgery. The neat, the precise, the anatomical attracted him, and he derived much pleasure from his practice of abdominal and reconstructive surgery and from urology; but neurosurgery became his true love. This specialty he developed step by step from zero, beginning with attempts to relieve the hopeless cases admitted to Stobhill for terminal care. In less than ten years he changed his wards from what was derisively called the 'deid hoose' to a teaching unit."

The worth of Paterson's work in neurosurgery was soon recognised, and he was appointed neurosurgeon to the Victoria Infirmary. He continued to work there until the establishment of the neurosurgical unit at Hillearn in 1940. When the National Health Service was started, he gave up general surgery—not without much heart-searching—and confined himself to neurosurgery.

E. A. T., once one of his students, writes:

"Two things were noteworthy about Eric Paterson. The first was that he was a great man. With the cultivation of a new specialty he combined modesty, enthusiasm, unmitigated frankness about himself even more than about others, unvarying truthfulness, and an uncanny habit of being right in his judgments. These are not the qualities which produce an overblown reputation during a man's lifetime, but they indicate the second noteworthy feature about him, which was that his greatness was not as widely known as might have been expected. Instead he built a solid foundation of friendship, respect, and those ultimates in admiration—emulation and imitation. He threw away opportunities to be grandiose, he gave limelight to juniors, and he demanded no ceremony. Such attributes are looked back on after years with love. Even his faults were venial, for though his irascibility towards foolishness was legendary he was never hurtful. His influence will outlast more brittle reputations. Nor for generations will the personal magnetism of the man fade from the minds of his pupils, and his pupils' pupils: for even longer the traditions of the units they serve must reflect the imprint of his character."

S. A. sends a physician's tribute:

"Wee Pat was really known and understood by only the surgeons. This was entirely proper. He belonged to them. Maybe physicians—second to none in their admiration for him—like to imagine this frail little man cast in a different role. To them it seemed strange that a surgeon should flit through the world on tiptoe—eager, tireless, and radiant. His face—specs and all—was a classic for the students sensitive to the physiognomy of intellect. Few men revealed in their demeanour, voice, and gesture so vivid a spectrum of human emotions: the tranquillity of deep meditation, the turbulence of the exploring mind, the flash of anger, and the smoulder of despair. But most memorable of all was his dazzling smile—impish and mischievous—transforming the senior surgeon into a jubilant schoolboy, but eloquent too of his deep humanity. James Eric was splendidly endowed with the attributes shared by the artist and the philosopher-surgeon: he was in love with the world of beauty; and its glory and splendour were reflected in his imagination. Out of these his riches he gave abundantly to patient and colleague alike: they rejoice in his talents; they grew and were fortified by his example."

W. G. also writes of the man as well as of the surgeon:

"Wee Pat's knowledge of surgical literature was immense, but surgery by no means filled his life. He regarded the world with childlike wonder so that all things were of interest to him. In literature, poetry, biography, music, and philosophy he was astonishingly well informed. Botany and geology were his delight. Sailing was a pleasure with him till it became too strenuous for his years, and then he turned to painting. Critical as he was of his own efforts here, he developed his not inconsiderable talents to the full by his customary intense application. Because of all his interests he was self-contained, and boredom was unknown to him, but he loved to meet a fellow enthusiast and made many friends through his hobbies.

"In his earlier years his sensitivity and his enthusiasm made him a little prickly and intolerant, but the passage of time wore away the sharp edges and left a benign, mature personality as stimulating as ever. He had no ambition to order other people's lives, and as a committee man he was a self-confessed failure. He could not tolerate scheming and lobbying.

"When he retired many groups of friends and associates gave him dinners and presentations. The Wee Man was deeply touched and quite bewildered by these tokens. His modesty had never allowed him to guess his own greatness nor to realise that he had gained 'that which should accompany old age, as honour, love, obedience, troops of friends'."

Mr. Paterson leaves a widow and two sons, one of whom is in general practice at Forres.

Mr. C. W. KIMBELL

G. C. S. writes:

"It was in the unpleasant circumstances of the 1940 campaign and then in captivity that Kim's sterling quality of character showed itself in all its brilliant clarity. His devoted care of the wounded prisoners and his unswerving loyalty to those who served with him were an inspiration to all. Small wonder that he had a host of friends who remember with affection and admiration his generosity and kindliness: and his inimitable conspiratorial chuckle. To all those the world is now a colder place."

Notes and News

WORLD HEALTH ORGANISATION

AT a meeting in Geneva of the W.H.O. Executive Board, which opened on Oct. 25,[1] Dr. V. Butrov (U.S.S.R.) stated that the U.S.S.R. would give 2 million roubles in 1961, in addition to its previous contribution, to the malaria eradication special account. The Board decided to recommend to the next World Health Assembly that part of the cost of the malaria eradication programme should be financed from the regular budget. The Board recommended a supplementary budget for 1961 of $800,000. This includes $100,000 for W.H.O. assistance to the Congo; a further $2,700,000 for the same purpose will be provided by the United Nations.

The Board commended Dr. M. G. Candau, the Director General of W.H.O., for the promptness and efficiency of W.H.O. assistance, and requested that it should continue. They also thanked the International Committee of the Red Cross, the League of Red Cross Societies, and Governments which had helped with the emergency health programme.

MENTAL ILLNESS IN SCOTLAND

AT the end of 1959 [2] the total number of people in Scotland who were under care for mental illness was 20,682 (467 fewer than at the end of 1958). Of those in mental hospitals (including the State Mental Hospital at Carstairs) 14,022 were certified patients (922 fewer than at the end of 1958) and 6385 were voluntary patients (472 more than at the end of 1958). The number of admissions (excluding transfers) during 1959 was 12,428 (990 more than in 1958). Admissions of voluntary patients increased by 1175 to 9977 (80% of the total), but admissions of certified patients dropped by 188 to 2451. 8719 voluntary patients (1095 more than in 1958) left hospital during the year. Discharges of certified patients (including discharges "by escape") numbered 1935 (118 more than in 1958) of whom about two-thirds were classified as "recovered".

At the end of 1959, the total number of certified mental defectives was 8421 (98 more than at the end of 1958). Of these 5107 were in institutions and 2466 under guardianship. Admissions of certified defectives to institutions during 1959 numbered 445 (53 more than in 1958). 234 patients were also admitted on an informal basis and 29 patients were transferred from certified to informal status. The number placed under guardianship was 111 (8 fewer than in 1958). 215 were discharged from compulsory detention (including those discharged "by escape").

A special study of readmissions during 1959 showed that of all admissions during the year 4480 (36%) were of patients with a previous admission. 1139 were readmitted within three months of last discharge, 886 (7%) within six months, 624 within nine months, and 365 within a year.

A NOVEL CLINICAL TRIAL

THE ethics of clinical trials can raise heated discussions wherever doctors meet, whether in lecture hall, laboratory, operating-theatre, hospital common-room, or students' hostel. Now, perhaps because his pseudonym covers a man with an F.R.C.S., Mr. John Rowan Wilson has made a medical version of the dilemma of means and ends the centre of his novel, *Double Blind*.[3]

A young bacteriologist is carrying out on a tropical island a double-blind trial with a vaccine against a form of encephalitis. The trial is being financed by a German drug firm which hopes to patent part of the manufacturing process. The island is an isolated primitive community under the tutelage of the Colonial Office. In obtaining permission to carry out the trial in its hospitals and clinics official channels have been by-passed. Though the natives normally give their permission before receiving the vaccine, it is unlikely that they realise the significance of the request. On the other hand, "South Atlantic" encephalitis is an endemic and dangerous infection and its control would be an enormous benefit to the community. Two deaths occur which may or may not be due to the vaccine. A Catholic priest complains. The Colonial Office, uneasily aware of lapses in protocol, if not in morality, send out a doctor to report on the trial.

This complex epidemiological situation contains many of the important issues which beset the conscience of the research worker. It is further complicated by the tense personal relations of the doctor, the bacteriologist, and his wife. Their personal problems are solved by the novelist's manipulation of the plot. The questions of general principle inevitably remain unsolved, but it is to their intelligent presentation that the book owes much of its unusual interest.

BIOLOGICAL ENGINEERING SOCIETY

THE first scientific meeting of this society was held on Oct. 15 at the National Institute for Medical Research, Mill Hill. In his opening address, Sir Charles Harington drew a parallel between the state of biological engineering today and biochemistry half a century ago. Perhaps in the years to come, he said, a fusion of the two disciplines of biology and engineering might result in biological engineering becoming as acceptable as biochemistry today. In the meantime, advances in biological and medical science depended greatly on advances in engineering and instrumentation, and the society was making a valuable contribution by enabling biologists and engineers to work more closely together. Prof. R. F. Woolmer, the president of the society, thought it appropriate that this first meeting should be held at the Institute, for its work and organisation was a good example of the way in which engineers could work together with biologists. About 100 people attended the meeting, and the programme of demonstrations was planned to give a cross-section of the subjects which the society hopes to cover.

SPASTIC SCHOOL-LEAVERS

ONE of the most useful qualities of voluntary organisations is their refusal to leave fairly well alone. The British Council for the Welfare of Spastics, now that they are satisfied that there is no longer a general shortage of school places for spastics, have turned their attention to the difficulties which these young people face when they go out into the world.[1] A pilot survey made by the council gives a depressing picture.

Of 34 recent school-leavers only 9 were thought to be capable of becoming fully self-supporting. Though 7 of these were in work only 3 were in jobs with reasonable prospects. None had received any training. Another group of 16 were described as "doubtfully employable", and of these 5 were in jobs and 5 awaiting training. None are ever likely to become financially independent. The remaining 9 were expected to be unemployable.

Thus, in all, only 12 were employed and not in very satisfactory jobs. The highest wage earned was £5 10s., and even those of average intelligence were doing work well below their capabilities. Of the 22 who are not in jobs some are in institutions or awaiting admission. Others live at home and some attend occupation centres. Some are waiting for training. All are thoroughly under-occupied and lack enough interests to fill their days, and this leads to mental and physical deterioration. In or out of jobs, they seem to lack friends and social life. Clubs for the handicapped do not attract them, for whether practicable or not, they want to go out to work like other youngsters. They seem to lack realism about their capabilities and of standards in the outside world, perhaps because of the inevitably sheltered atmosphere of the schools in which they were educated.

The numbers in the survey are small, and the Council offer the results not as a basis for recommendations but as evidence of need. The results are a salutary reminder that, like the rest of us, the handicapped are living longer and that the support we give them must be continuous and flexible, keeping pace with their changing ages and circumstances.

1. See *Lancet*, Nov. 5, 1960, p. 1037.
2. Report of General Board of Control for Scotland for the year 1959. H.M. Stationery Office. Cmnd. 1160. 1960. Pp. 33. 2s. 6d.
3. The Double Blind. JOHN ROWAN WILSON. London: Collins. 1960. Pp. 256. 16s.

1. Annual report 1959-60. The address of the Council is 13, Suffolk Street, Haymarket, London, S.W.1.

University of Cambridge

On Oct. 29 the following degrees were conferred:

M.D.—P. A. J. Ball, J. H. Cule, P. C. Gautier-Smith, J. C. Kelsey, C. G. Rob (by proxy), David Wise.
M.B.—T. J. Willis.

University of Birmingham

Dr. R. L. Edwards has been appointed senior lecturer and first assistant in the department of obstetrics and gynæcology.

University of Glasgow

On Nov. 5 the degree of M.D. was conferred on William Cullen (with commendation) and on Joseph Sluglett.

University of Queensland

Dr. T. J. Rendle-Short, lecturer in child health in the University of Sheffield, has been appointed to the newly established chair of child health in this university.

Royal College of Physicians of London

Dr. K. D. Keele will give the FitzPatrick lectures on Tuesday, Nov. 29, and Thursday, Dec. 1, at 5 P.M., at the college, Pall Mall East, S.W.1. His subject will be Evolution of Clinical Methods in Medicine.

Royal College of Physicians of Edinburgh

A meeting of college was held on Nov. 1, with Dr. A. Rae Gilchrist, the president, in the chair.

A Hill Pattison-Struthers bursary for 1960 has been awarded to Dr. Philip Lanzkowsky and the Jean Hunter prize for 1960 to Dr. A. W. E. Soysa.

The following were elected to the fellowship:

Eric James, M. M. Whittet, Keshavarao Krishnarao Datey, H. G. H. Richards, H. R. L. Fraser, A. B. Hegarty, J. S. Robson, J. A. Loraine, Tadepalli Shamsunder Row, R. C. Jackson, Velva Schrire, Agnes L. Scott, B. C. Sinclair-Smith, A. C. Kennedy, John Butler, K. L. Stuart, Arthur Jarrett, A. R. Somner, D. S. Nand, S. L. A. Manuwa, J. H. Hutchison, D. F. Cappell, J. H. Walters, K. W. Donald, A. W. Woodruff, Eric Samuel.

The following were elected to the membership:

C. W. Kidd, A. P. Meiklejohn, R. M. Vanreenen, Krishna Rao Purohit, H. L. Davis, R. W. McConnachie, Thambippillai Vamadevan, A. R. Adams, N. R. Young, William McQuaker, Sean O'Reilly, L. H. Harris, D. G. B. Powell, David Jacobson, Elaine M. Belton, Ralph Emery, J. K. Binns, Sheikh Muhammad Haneef, Ram Singh, G. C. Timbury, Joseph Gatt, Barry Lewis, Anand Mohan Sur, R. G. B. Williamson, Hamdy Mahmoud El-Sayed, Samir Mohamed Omar Hilal, Mookencherry Cherian Mathews, A. I. Rae, Frank Tsu-Chang Hu, David Burrows, Nedumchalil Markose Mathai, Baboobhai Rambhai Patel, B. S. David, Achyut Govind Motiwale, Peter Taylor, N. P. Burns, Kishin Hingorani, J. D. Woolridge, Boon-Kheng Khoo, I. R. Lawson, Pandramajal Narayanappa Krishnamurthy, Khalid Haji Aboo Mitha, Nalkundad Kyathappanavara Channappa, R. A. Osborn, Dona Priyalatha Wijesinghe, M. D. Bowie, Lotfy Labib Basta, Vishnukumar Gupta, Erasmus Lynghdoh, M. G. Dunnigan, Iain Michie, Harischandra Ranasinghe, Ekpo Edet Eyo, Chenniah Javaraya Bhakta Ram, Krishnadhan Datta, Susil Chandra Munsi, Subrata Sen, Cheruveetil Kochukutty Gopi, Mohammad Ata, J. A. Waddell, Bhim Sen Ghisaram Singhal, Chandidas Gupta, Joseph Levin, E. S. Garnett, Gulamabbas Juma Ebrahim, W. H. S. George, J. A. McBride.

Heberden Society

Dr. J. J. Bunim will give a Heberden oration on Friday, Dec. 2, at 4.15 P.M., at the Wellcome Foundation, Euston Road, London, N.W.1. His subject will be a Broadened Spectrum of Sjögren's Syndrome and its Pathogenetic Implications.

North West Metropolitan Regional Hospital Board

Lord Moynihan has been appointed chairman of this board.

Albert Lasker Grants

The American Public Health Association have awarded grants to Dr. F. H. C. Crick, of Cambridge, and Dr. M. H. F. Wilkins, of London, for their work on processes governing heredity in living cells and viruses, and to Prof. Lionel Penrose for his contribution to the development of human genetics and his findings on the effect of nuclear and other radiation on human beings and their offspring.

On Wednesday, Nov. 16, at 5.15 P.M., at the Royal Free Hospital, Gray's Inn Road, London, W.C.1, Sir William Morrow, physician to the Royal Prince Alfred Hospital, Sydney, will speak on ulcerative colitis.

Applications are invited for grants for research into diabetes mellitus and associated diseases. Further particulars may be had from the secretary of the research grants committee of the Association, 152, Harley Street, London, W.1.

Diary of the Week

NOV. 13 TO 19

Monday 14th

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.12
4 P.M. Dr. Brian Ackner: Depressive Illness—Clinical Syndrome and Treatment.

INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5 P.M. Dr. P. D. Samman: Eccrine and Apocrine Glands in Health and Disease.

Tuesday, 15th

UNIVERSITY COLLEGE, Gower Street, W.C.1
5.30 P.M. Prof. J. H. Gaddum: Pharmacological Analysis of Tissue Extracts.

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) Dr. K. S. Kirby: Nucleic Acids and Cancer.

INSTITUTE OF OBSTETRICS
3 P.M. (Hammersmith Hospital.) Dr. Helen Payling Wright: Varicose Veins in Pregnancy.

ST. MARY'S HOSPITAL MEDICAL SCHOOL, W.2
5 P.M. (Wright-Fleming Institute.) Prof. Norman Morris: Human Relations in Obstetrics.

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, 91, Dean Street, W.1
5.30 P.M. Mr. G. C. Knight: Trigeminal neuralgia.

ROYAL ARMY MEDICAL COLLEGE, Millbank, S.W.1
5 P.M. Dr. Wilson, F.INST.P.: Nuclear Physics.

LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM
5.15 P.M. (General Infirmary at Leeds.) Dr. Bertram Selverstone (Boston): Modern Treatment of Gliomas.

MANCHESTER MEDICAL SOCIETY
4.30 P.M. (Medical School, University of Manchester.) *Medicine.* Dr. J. J. Bunim (Bethesda): Alkaptonuria and Ochronosis.

Wednesday, 16th

POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P.M. Dr. A. L. Greenbaum: Fat Metabolism.

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. Henry Haber: Clefts, Vesicles, and Bullæ.

INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Dr. J. N. Pattinson: Abnormalities of the Mediastinum.

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
8.15 P.M. *General Practice.* Dr. G. I. Watson, Dr. Samuel Leff, Prof. C. H. Stuart-Harris: Infectious Diseases Today.

HARVEIAN SOCIETY
8.15 P.M. (Joint meeting with the Osler Club at 11, Chandos Street, W.1.) Dr. A. White Franklin, Dr. Maurice Long, Dr. T. F. Cotton, Sir Geoffrey Keynes, Mr. A. Dickson Wright: Harvey and Osler.

UNIVERSITY OF LEEDS
5 P.M. (General Infirmary at Leeds.) Mr. G. W. Theobald: Gynæcological Pain.
6 P.M. Mr. J. B. Farquhar: Third State of Labour.

Thursday, 17th

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S.W.1
5 P.M. Prof. D. V. Hubble: The Endocrine Orchestra (Langdon-Brown lecture).

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine.) Dr. J. C. Kendrew: The Structure of Proteins.

BRITISH INSTITUTE OF RADIOLOGY, 32, Welbeck Street, W.1
8 P.M. Mr. J. B. Massey, Mrs. J. J. Gough, Dr. Walter Shanks, Dr. A. M. Jelliffe: Role of Moving Field Techniques in Treatment with High Energy Radiation.

NUFFIELD ORTHOPÆDIC CENTRE, Wingfield-Morris Orthopædic Hospital, Oxford
8.30 P.M. Mr. J. Crawford Adams: Ischio-Femoral Arthrodesis for Osteoarthritis and Tuberculous Arthritis of the Hip.

MANCHESTER MEDICAL SOCIETY
8 P.M. Sir Robert Macintosh: A Trip to Russia and China.

HONYMAN GILLESPIE LECTURE
5 P.M. (University New Buildings, Teviot Place, Edinburgh.) Prof. T. N. A. Jeffcoate: Functional Disorders of the Female Bladder and Urethra.

UNIVERSITY OF ST. ANDREWS
5 P.M. (Physiology Department, Queen's College, Dundee.) Mr. L. N. Pyrah: Use of the Loops of Small and Large Intestine in Urological Surgery.

Friday, 18th

UNIVERSITY OF LONDON
5.30 P.M. (University College.) Prof. M. Westergaard (Copenhagen): Some Fundamental Concepts and Problems in Molecular Genetics.

ROYAL SOCIETY OF MEDICINE
5.30 P.M. *Epidemiology and Preventive Medicine.* Dr. E. R. Hargreaves: Epidemiological Studies in Cornwall.

ROYAL MEDICO-PSYCHOLOGICAL ASSOCIATION
2.15 P.M. (1, Wimpole Street, W.1.) Dr. Eliot Slater: Hysteria 311 (Maudsley lecture.)

POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A.M. Mr. H. Osmond-Clarke: Cervical Disc Lesions.
4 P.M. Prof. C. E. Dent: Primary Hyperparathyroidism.

FACULTY OF RADIOLOGISTS, 47, Lincoln's Inn Fields, W.C.2
4.30 P.M. Prof. R. W. Scarff: Prognosis in Carcinoma of the Breast. (Skinner lecture.)

PLYMOUTH MEDICAL SOCIETY
8.30 P.M. (North Friary House.) Dr. Richard Asher: See How They Come.

Saturday, 19th

COLLEGE OF GENERAL PRACTITIONERS
11.30 A.M. (B.M.A. House, W.C.1.) Dr. Lindsey Batten: The Medical Adviser. (James Mackenzie lecture.)